I) Antimicrobial Agents

(INFECTIOUS DISEASES)

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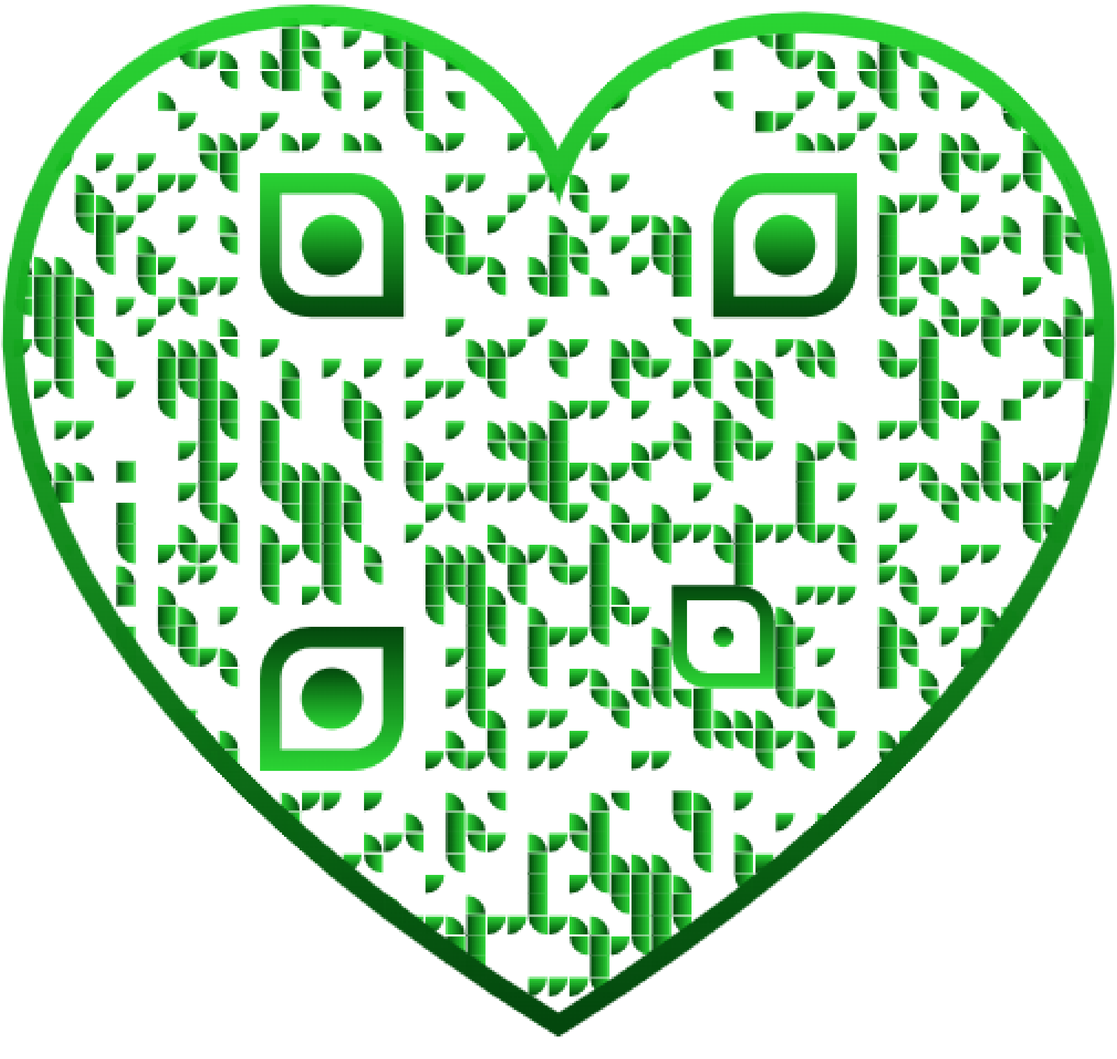


Introduction

➢ History of Antimicrobial Agents:-

* **Paul Ehrlich** (14 March 1854 – 20 August 1915);

- In the *early* **1900s**, the **German physician** and **scientist Paul Ehrlich** discovered **Arsphenamine** (**Salvarsan®**) [*Organoarsenic compound*], the ***first* effective chemotherapeutic agent** in the *treatment of* **syphilis**.
- It was marketed under the trade name **Salvarsan®** in **1910**.
- **Neosalvarsan®** (**Neoarsphenamine**), which was ***more* soluble** and ***less* side effects**, and it became *available in* **1912**.
- **In 1908**, he received the **Nobel Prize** in Physiology or Medicine for his "*work on immunity*".

Neosalvarsan
Neosalvarsan
Neosalvarsan
Solución de lactosa

Paul Ehrlich
(1854 –1915)

* **Sir Alexander Fleming** (6 August 1881 – 11 March 1955);

- In **Friday 28 September 1928**, the ***Scottish scientist*** **Alexander Fleming** *returned* from holiday and examined some **old plates** of *staphylococci* in his research laboratory at **St. Mary's Hospital in London**.
- He observed that ***contaminating mold growth*** (subsequently identified as a strain of *Penicillium notatum*) ***inhibited*** **staphylococcal growth** on **one plate**.
- Further experimentation showed that **Penicillin** from the mold was ***antibacterial against*** *streptococci*.
- **In 1940**, **Fleming** and his team of researchers at **Oxford University** under the direction of **Howard Florey** and **Ernst Chain** was ***purified*** and ***concentrated*** **Penicillin** and reported its success as an **antimicrobial agent** ***against*** *streptococcal* infections in mice.
- **In 1942**, ***survivors*** of the **Cocoanut Grove fire** in **Boston** were the ***first*** **burn patients** to be ***successfully treated*** with **Penicillin**.
- **Fleming**, **Florey** and **Chain** were awarded the **Nobel Prize** in Physiology and Medicine in **1945**.

Sir Alexander Fleming
(1881–1955)

Ernst Boris Chain
(1906–1979)

Howard Florey
(1898-1968)

Cocoanut Grove Fire in 1942

* **Gerhard Domagk** (30 October 1895 – 24 April 1964);

- A ***few* decades later**, **German scientists Josef Klarer**, **Fritz Mietzsch**, and **Gerhard Domagk** *discovered* the **antibacterial activity** of a synthetic dye, **prontosil®**, that could treat *streptococcal* and *staphylococcal* infections in mice.
- **Prontosil®** is an **antibacterial drug discovered** in **1932** by a research team at the **Bayer** *Laboratories*.
- **Prontosil®** is first **sulfonamide drug** and opened a new era in medicine.
- **Domagk** was awarded the **Nobel Prize** in Medicine in **1939** for his work.
- The ***success*** of the **sulfa drugs** ***led to*** the **discovery** and **production** of **additional *important* classes** of **synthetic antimicrobials**.

Gerhard Domagk
(1895 – 1964)

* **Selman Waksman** (July 22, 1888 – August 16, 1973);

- In the **1940s**, **Selman Waksman**, a ***prominent*** **soil microbiologist** at **Rutgers University**, led a research team that ***discovered*** **several antimicrobials**, including **Actinomycin**, **Streptomycin** and **Neomycin**.

Microbiology

➢ Types of Organisms:-

A) Eukaryotic; is ***any* organism** whose **cells** have a **nucleus** and ***other organelles*** *enclosed within* **membranes. Eukaryotic cells** *such as* in **Animal**, **Plant**, **Fungal** and **Protista cells**.

Nucleus; Present

Cell wall; Only in plant cells and fungi.

Mitochondria; Present

Golgi apparatus; Present

Lysosomes; Present

Microtubules; Present

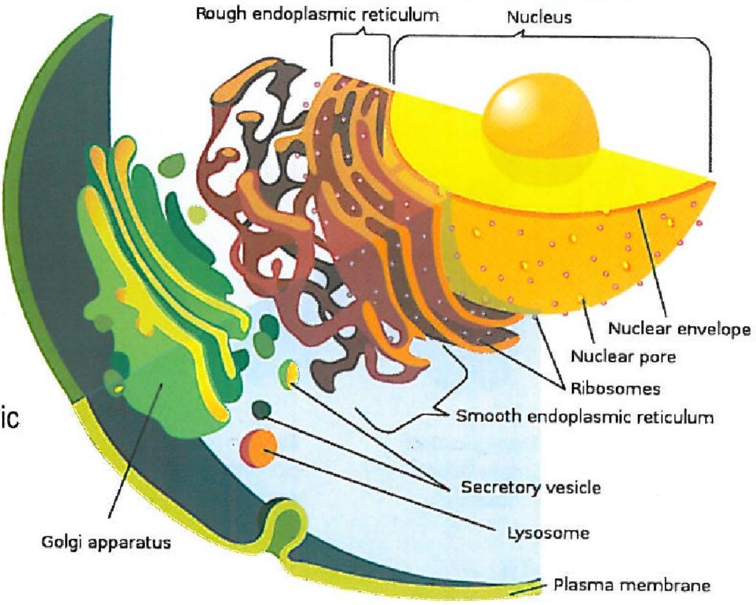
Cytoskeleton; Present

Ribosomes; Larger than prokaryotic

Endoplasmic reticulum; Present

Chromosomes; More than one.

Cell size; 10-100 µm


Rough endoplasmic reticulum
Nucleus
Nuclear envelope
Nuclear pore
Ribosomes
Smooth endoplasmic reticulum
Secretory vesicle
Lysosome
Golgi apparatus
Plasma membrane

B) Prokaryotic; is a ***unicellular*** **organism** that *lacks* a **nucleus, mitochondria**, or ***any other*** **membrane-bound organelle**; **Prokaryotic cells** *such as* in **Bacteria** and **Archaea cells**.

Nucleus; Absent

Cell wall; Present and complexed.

Mitochondria; Absent

Golgi apparatus; Absent

Lysosomes; Absent

Microtubules; Absent or rare

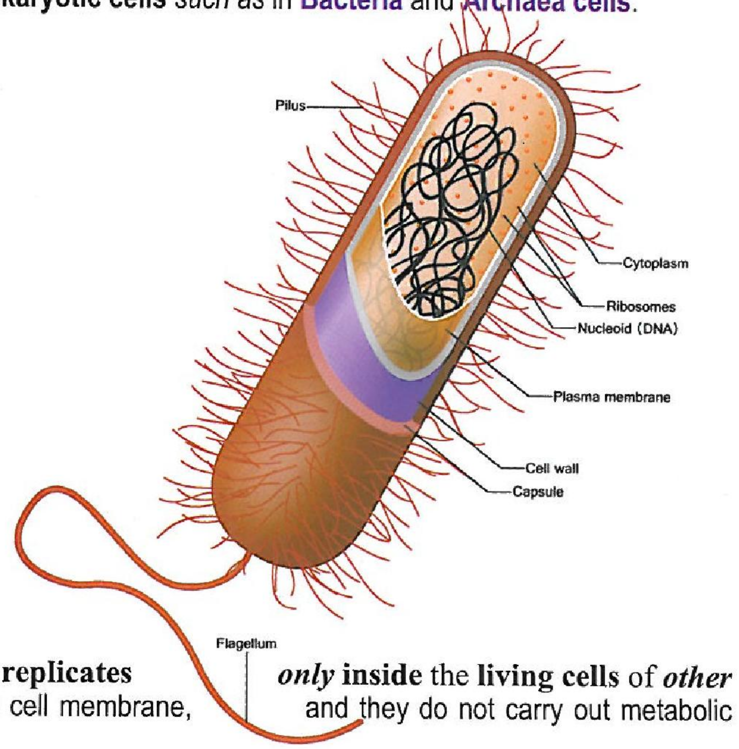
Cytoskeleton; May be absent

Ribosomes; Smaller than eukaryotic

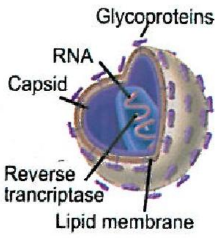
Endoplasmic reticulum; Absent

Chromosomes; One (Plasmids)

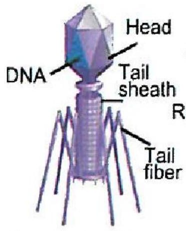
Cell size; 1-10 µm


Pilus
Cytoplasm
Ribosomes
Nucleoid (DNA)
Plasma membrane
Cell wall
Capsule
Flagellum

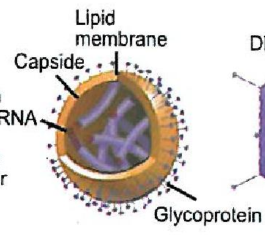
C) Virus; is a ***small infectious* agent** that **replicates** ***only*** **inside** the **living cells** of ***other organisms***; They lack both a cell wall & a cell membrane, and they do not carry out metabolic processes.


Glycoproteins
RNA
Capsid
Reverse trancriptase
Lipid membrane

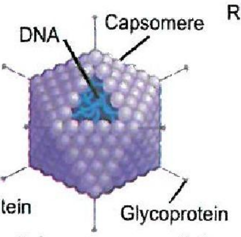
HIV


Head
DNA
Tail sheath
Tail fiber

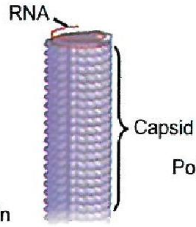
Bacteriophage


Lipid membrane
Capside
RNA
Glycoprotein

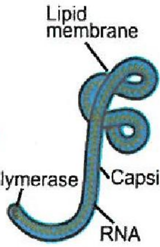
Influenza Virus


DNA
Capsomere
Glycoprotein

Adenovirus

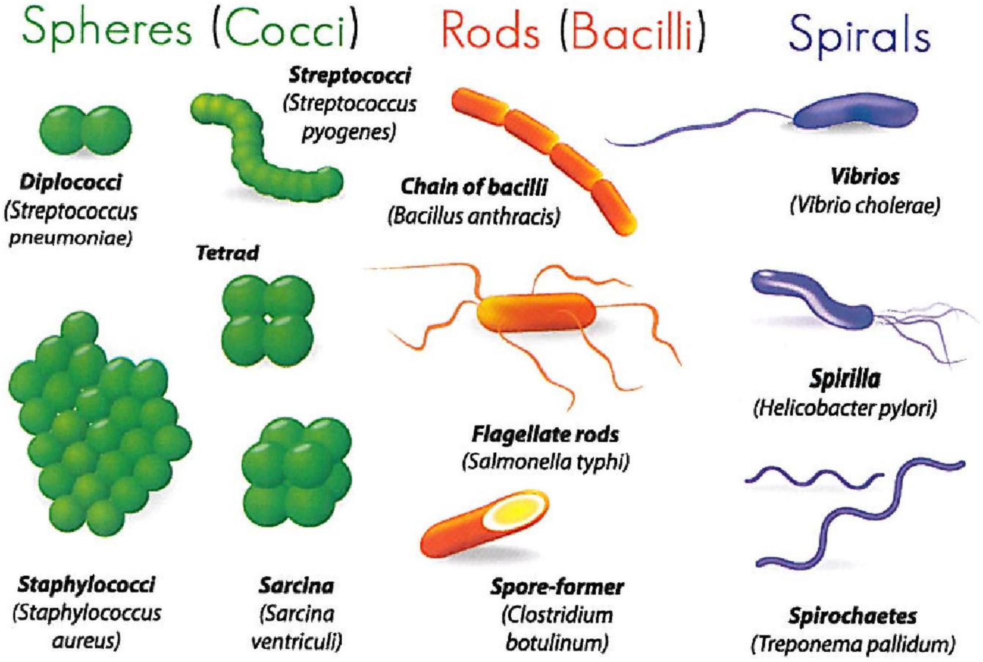


Tobacco Mosaic Virus


Lipid membrane
Polymerase
Capsid
RNA

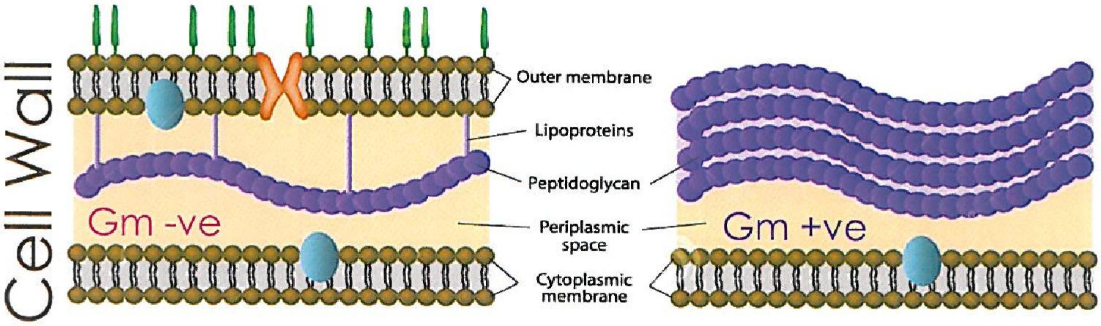
Ebola Virus

➢ Shapes and Arrangements of Bacteria:-

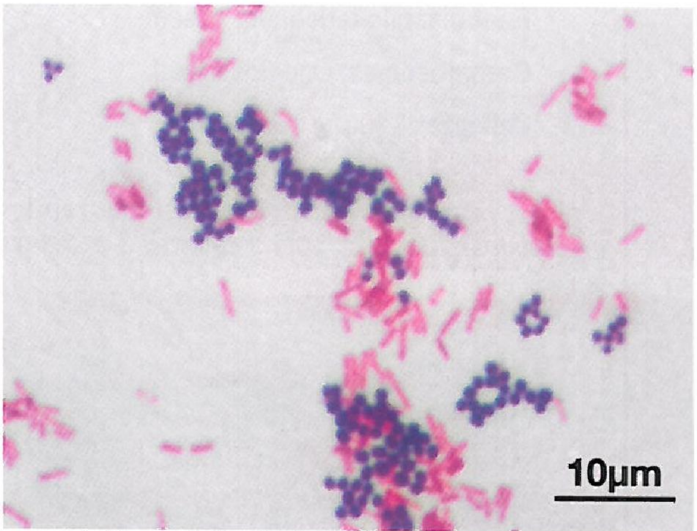

Spheres (Cocci)
Rods (Bacilli)
Spirals
Streptococci
(Streptococcus pyogenes)
Diplococci
(Streptococcus pneumoniae)
Tetrad
Chain of bacilli
(Bacillus anthracis)
Vibrios
(Vibrio cholerae)
Spirilla
(Helicobacter pylori)
Flagellate rods
(Salmonella typhi)
Staphylococci
(Staphylococcus aureus)
Sarcina
(Sarcina ventriculi)
Spore-former
(Clostridium botulinum)
Spirochaetes
(Treponema pallidum)

➢ Gram Stain:-

- Gram stain is a ***method*** of **staining** used to ***differentiate*** **bacterial species** into **two large** groups (Gram +ve & Gram -ve);
- The name comes from the *Danish bacteriologist* **Hans Christian Gram**, who developed the technique in 1884.
- Gram staining ***differentiates*** **bacteria** by the chemical and physical properties of their **cell walls**; by *detecting* **Peptidoglycan**.


Cell Wall
Outer membrane
Lipoproteins
Peptidoglycan
Periplasmic space
Cytoplasmic membrane
Gm -ve
Gm +ve

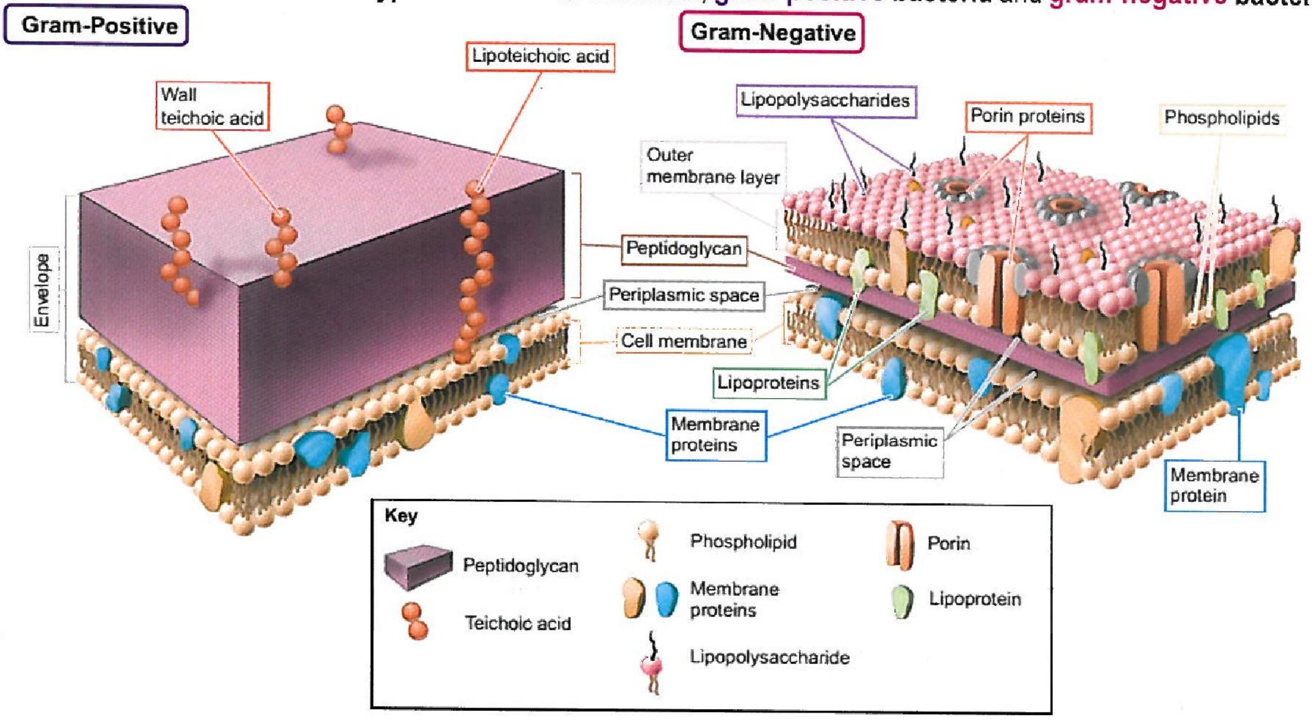
- **Gram positive** bacteria; **thick layer** of **peptidoglycan** (*about* 90% of cell wall).
- **Gram negative** bacteria (**thin layer** of **peptidoglycan** (*about* 10% of cell wall).
- **Gram positive** bacteria ***retain*** the **crystal violet dye**, while the **Gram-negative** bacteria ***do not***; *after* **washing** by **organic solvent** such as **alcohol** (*extracts* the **blue dye complex** ***from*** the **lipid-rich**, **thin layer peptidoglycan** **gram negative** **bacteria**), a ***counterstain*** is **added** (**Safranin** or **Fuchsine**) that *will* **stain** these **Gram-negative** bacteria a **pink color**.



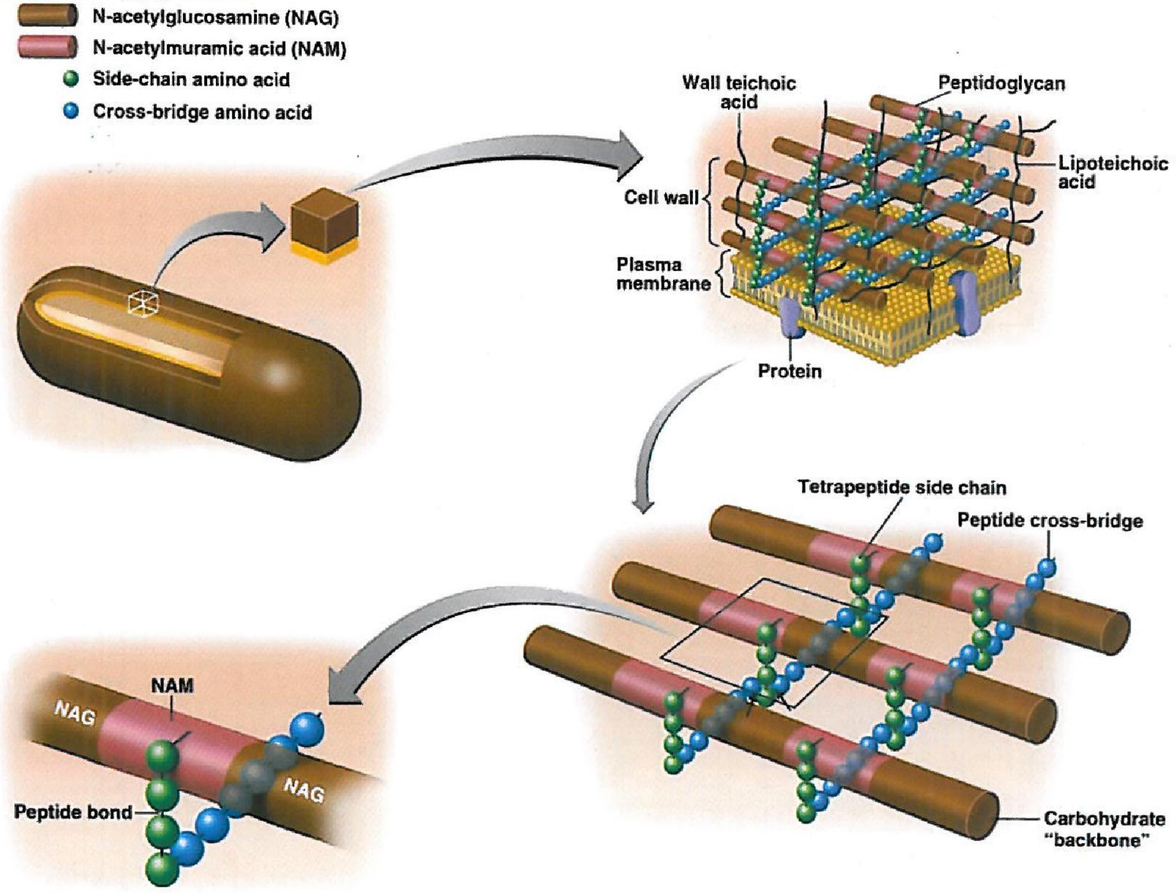
A **Gram stain** of mixed *Staphylococcus aureus* (**gram-positive** cocci, in **violet**) and *Escherichia coli* (**gram-negative** bacilli, in **pink**)

➢ Bacterial Cell Wall:-

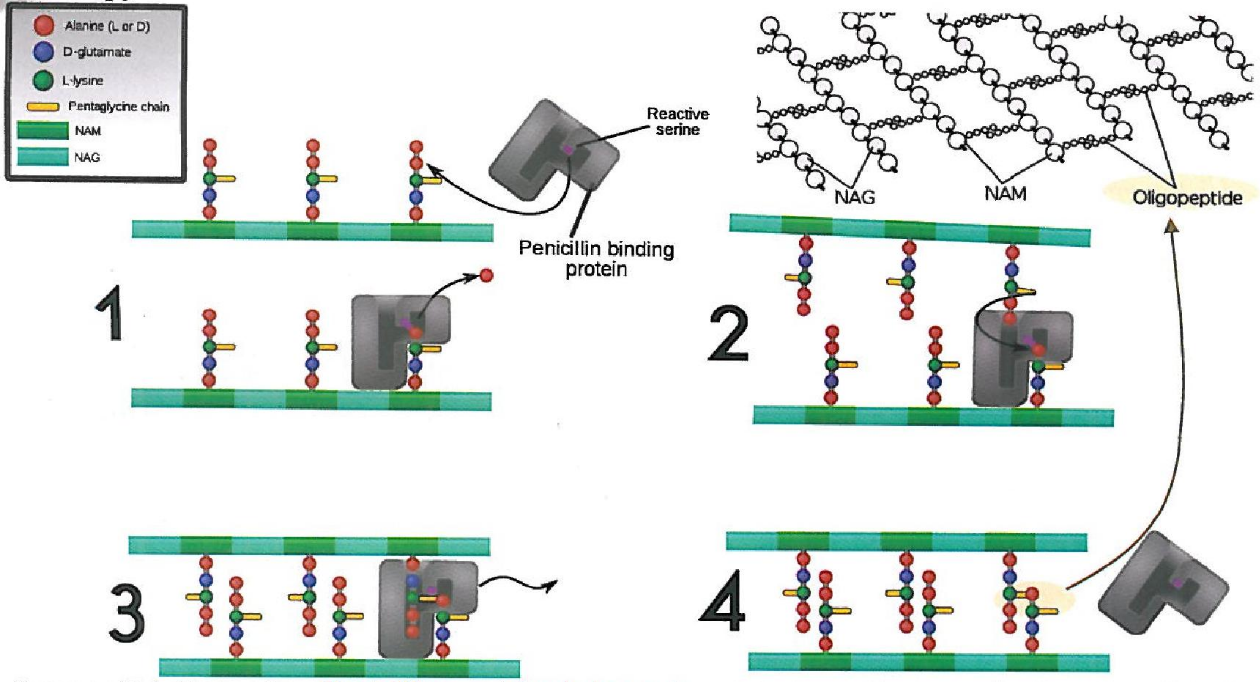
- There are **two** ***main types*** of **bacterial cell walls**; **gram-positive** bacteria and **gram-negative** bacteria.


Gram-Positive
Gram-Negative
Lipoteichoic acid
Wall teichoic acid
Envelope
Lipopolysaccharides
Porin proteins
Phospholipids
Outer membrane layer
Peptidoglycan
Periplasmic space
Cell membrane
Lipoproteins
Membrane proteins
Periplasmic space
Membrane protein
Key
Peptidoglycan
Teichoic acid
Phospholipid
Membrane proteins
Lipopolysaccharide
Porin
Lipoprotein

➢ Peptidoglycan:-


N-acetylglucosamine (NAG)
N-acetylmuramic acid (NAM)
Side-chain amino acid
Cross-bridge amino acid
Wall teichoic acid
Peptidoglycan
Lipoteichoic acid
Cell wall
Plasma membrane
Protein
Tetrapeptide side chain
Peptide cross-bridge
Carbohydrate "backbone"
NAM
NAG
NAG
Peptide bond

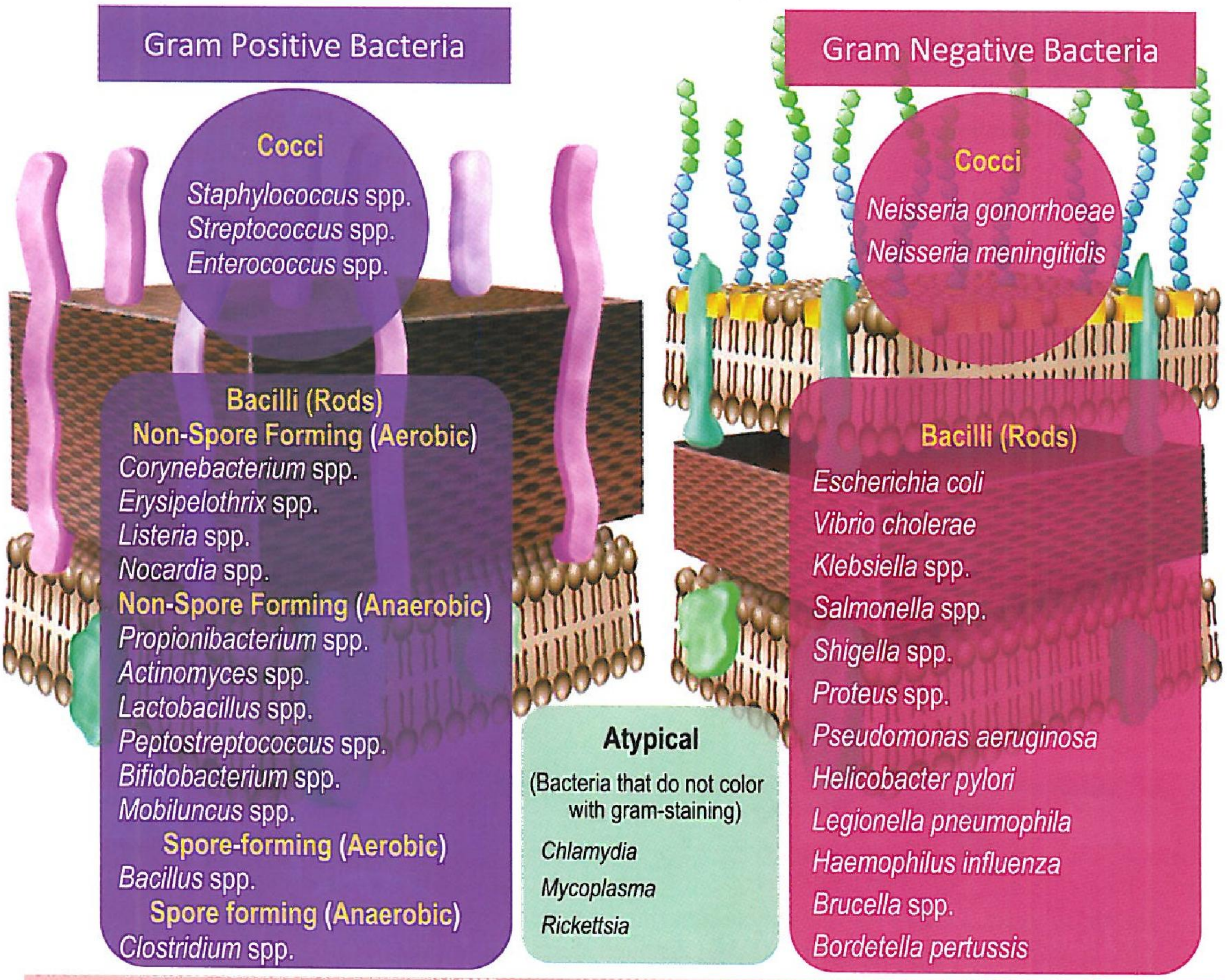
- **Peptidoglycan** is ***made up*** of a **polysaccharide backbone** consisting of alternating **N-Acetylmuramic acid (NAM)** and **N-Acetylglucosamine (NAG)** residues in **equal amounts**.
- **Peptidoglycan** is ***responsible for*** the ***rigidity*** of the **bacterial cell wall** and for **cell shape**.
- **Penicillin-binding proteins (PBPs)** are a ***normal constituent*** of **many bacteria**, which are ***essential for*** **final stage** of **bacterial cell wall** ***synthesis*** (form the **bonds** ***between*** **oligopeptide** ***crosslinks*** in **peptidoglycan**).
- **PBPs** are ***members*** of a **subgroup** of **enzymes** ***called*** **Transpeptidases**.



Some* antibiotics** such as **Penicillins** and **Cephalosporines** ***interfere with the ***production*** of **peptidoglycan** by ***binding to*** **penicillin-binding proteins enzymes** (**Transpeptidases enzymes**).

➢ Classification of Bacteria:-

- **According to Gram Stain**;



Gram Positive Bacteria

Cocci

Staphylococcus spp.
Streptococcus spp.
Enterococcus spp.

Bacilli (Rods)

Non-Spore Forming (Aerobic)

Corynebacterium spp.
Erysipelothrix spp.
Listeria spp.
Nocardia spp.

Non-Spore Forming (Anaerobic)

Propionibacterium spp.
Actinomyces spp.
Lactobacillus spp.
Peptostreptococcus spp.
Bifidobacterium spp.
Mobiluncus spp.

Spore-forming (Aerobic)

Bacillus spp.

Spore forming (Anaerobic)

Clostridium spp.

Atypical

(Bacteria that do not color with gram-staining)

Chlamydia
Mycoplasma
Rickettsia

Gram Negative Bacteria

Cocci

Neisseria gonorrhoeae
Neisseria meningitidis

Bacilli (Rods)

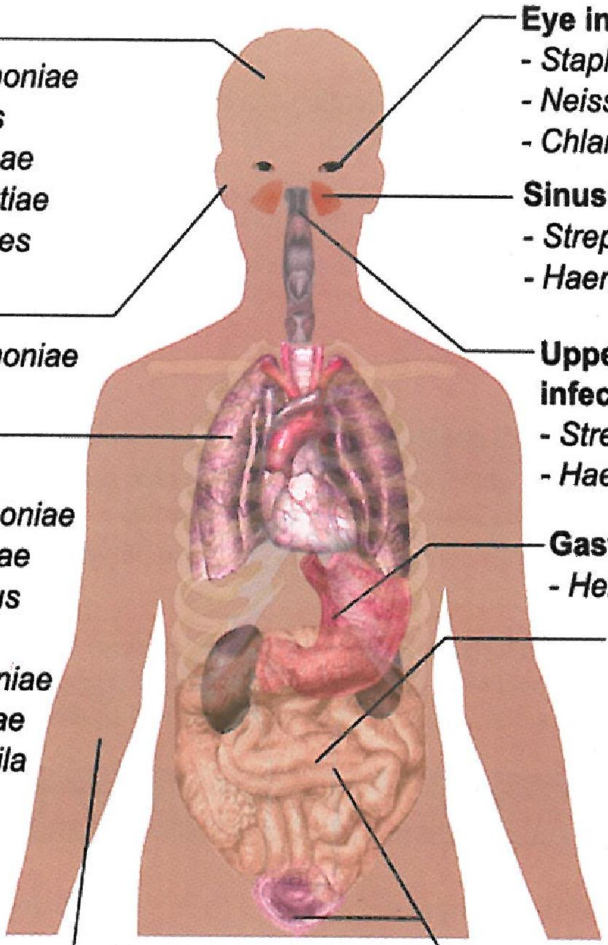
Escherichia coli
Vibrio cholerae
Klebsiella spp.
Salmonella spp.
Shigella spp.
Proteus spp.
Pseudomonas aeruginosa
Helicobacter pylori
Legionella pneumophila
Haemophilus influenza
Brucella spp.
Bordetella pertussis

Mycobacteria

Mycobacteria a genus of ***rod-shaped*** **acid-fast bacteria** having ***two significant*** **pathogenic species**;

- ***Mycobacterium leprae***; leprosy. - ***Mycobacterium tuberculosis***; **tuberculosis**.

- **According to Site of Infection**;



Bacterial meningitis
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Streptococcus agalactiae*
- *Listeria monocytogenes*

Otitis media
- *Streptococcus pneumoniae*

Pneumonia
Community-acquired:
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*

Atypical:
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Legionella pneumophila*

Tuberculosis
- *Mycobacterium tuberculosis*

Skin infections
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Pseudomonas aeruginosa*

Sexually transmitted diseases
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Treponema pallidum*
- *Ureaplasma urealyticum*
- *Haemophilus ducreyi*

Eye infections
- *Staphylococcus aureus*
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*

Sinusitis
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

Upper respiratory tract infection
- *Streptococcus pyogenes*
- *Haemophilus influenzae*

Gastritis
- *Helicobacter pylori*

Food poisoning
- *Campylobacter jejuni*
- *Salmonella*
- *Shigella*
- *Clostridium*
- *Staphylococcus aureus*
- *Escherichia coli*

Urinary tract infections
- *Escherichia coli*
- Other Enterobacteriaceae
- *Staphylococcus saprophyticus*
- *Pseudomonas aeruginosa*

Antimicrobial Therapy

- **Empiric Therapy** (based on experience):-
  - **Initial** or **Blind** or **Umbrella** or **Empirical therapy** *refers to* the **treatment** of an **infection** *without knowing* the **causative pathogen**.
  - **Initial Antibiotics** are *given* to a **person** *until* **laboratory confirmation**, **treatment** *may be* ***changed*** to a *more* **specific antibiotic**.
  - *Example*; **Community-acquired pneumonia** can also be *treated* **empirically**—with a **Macrolides** or **Fluoroquinolones**, *without* **performing specific diagnostic testing**.
- **Definitive Therapy** (*Pathogen-specific*):-
  - *Once* the **infecting organisms** has been *identified*, the **specific antibiotic** ***should be*** **narrow spectrum** to; 1) *Reduce* **cost**.
    2) *Reduce* **toxicity**.
    3) *Prevent* **antimicrobial resistance**.
- **Prophylactic Therapy:-**
  - *Administration* of **antimicrobials** in *absence* of a **known infection**, to decrease the risk of infection.
  - *Example*; 3^{rd} **generation cephalosporins** in *surgical* **wound**.

Bacteriostatic and Bactericidal

Bacteriostatic:-

- A **drug** that ***inhibits*** **growth** and **replication** of a **bacteria** ***without*** **killing it**, thus limiting the spread of infection until the immune system attacks, immobilizes and eliminates the pathogen.
- Bacteriostatic drugs depend upon the immune system of the patient for activity, and so make for a poor choice where the immune system is compromised, for example patients with AIDS.
- ***Example***; **Sulfonamides**, **Tetracyclines** and **Macrolides**, act by ***inhibiting*** **protein synthesis**.
- **Minimum Inhibitory Concentration** (**MIC**); is the ***minimum*** **concentration** of **drug** which can ***inhibit*** the ***growth*** of the **microorganism**.

Bactericidal:-

- A **drug** that ***directly*** **kills** a **bacteria**.
- *Example*; **Drugs** that *primarily act* on the **cell wall** (e.g.; **β-lactams**), **cell membrane** (e.g.; **Daptomycin**), or **bacterial DNA** (e.g.; **Fluoroquinolones**).
- **Minimum Bactericidal Concentration** (**MBC**) is the ***minimum concentration*** of **drug** which can ***kill*** the **microorganism**.

- **N.B.**; although practical, this classification may be too simplistic because it is ***possible*** for an **antibiotic** to be **bacteriostatic** ***for*** **one organism** and **bactericidal** ***for*** **another**. For example, **Linezolid** is **bacteriostatic against** *Staphylococcus aureus* and *enterococci* but is **bactericidal against** most strains of *S. pneumoniae*.

Factors Affecting Selection of Antimicrobial Agents

1) Identity of the Pathogen

2) Site of Infection

3) Patient Factors

4) Pharmacokinetics

5) Antimicrobial Safety

6) Cost

1) Identity of the pathogen;

- ***Identifying*** the **organism** is ***important to*** **selection** of the ***specific*** **antimicrobial agent**.

2) Site of infection;

- **Adequate concentrations** of **antimicrobials** ***must be*** **delivered to** the **site of infection**.
- **Lipid solubility** of a **drug** is a ***major determinant*** of its ***ability*** to **penetrate** *into the* **brain**.
- **Molecular weight** of the **drug**; ***low molecular*** **weight** has an ***enhanced*** **ability** to ***cross*** the **blood–brain barrier**, ***high molecular*** **weight** (such as; **Vancomycin**) ***penetrate*** **poorly**, even in the ***presence*** of **meningeal** ***inflammation***.
- **Protein binding of the drug**; ***high degree*** of **protein binding** of a drug ***restricts*** its ***entry*** *into the* **CSF**.

3) Patient factors;

- **Immune system**; **HIV infection**, **alcoholism**, **diabetes**, **malnutrition**, **autoimmune diseases**, **pregnancy** or **advanced age** can affect a **patient's immune-competence**, as can **immunosuppressive drugs**. ***High doses*** of **bactericidal agents** or ***longer courses*** of **treatment** may be *required to* ***eliminate*** **infective organisms** in ***these*** **individuals**.
- **Renal function**; ***Poor*** **kidney function** may cause ***accumulation*** of *certain* **antibiotics** (such as; **Vancomycin** and **Aminoglycosides**). **Dosage adjustment** ***may*** **require**.
- **Hepatic function**: **Antibiotics** that are ***concentrated*** or ***eliminated by*** the **liver** (such as; **Erythromycin** and **Doxycycline**) ***must be*** used *with* **caution** when ***treating*** **patients** with **liver dysfunction**.

- **Perfusion**: ***Decreased*** **circulation** to an **anatomic area**, *such as* the **lower limbs** of a **diabetic patient**, ***reduces*** the **amount of antibiotic** that ***reaches*** that **area**, ***making these*** **infections** ***difficult*** to **treat**.
- **Age**:
  - **Newborns**; ***poorly*** **developed** of **renal** or **hepatic elimination**, ***toxic effects*** of **Chloramphenicol** and **Sulfonamides**.
  - **Young children**; ***should not*** be ***treated with*** **Tetracyclines** or **Quinolones**; which ***affect*** **bone growth** and **joints**.
  - **Elderly patients**; may have ***decreased*** **renal** or **liver function**, **Dosage adjustment** ***may*** **require** in ***certain*** **antibiotics**.
- **Pregnancy**: **Antimicrobials** ***easily crosses*** **placental barrier** and ***may*** **affect** the **fetus**.

FDA Categories of Antimicrobials and Fetal Risk

A	B	C	D	X
No human fetal risk or remote possibility of fetal harm	No controlled studies show human risk; animal studies suggest potential toxicity	Animal fetal toxicity demonstrated; human risk undefined	Human fetal risk present, but benefits may outweigh risks	Human fetal risk clearly outweighs benefits; contraindicated in pregnancy
	Penicillins Cephalosporins Aztreonam Clindamycin Erythromycin Azithromycin Metronidazole Nitrofurantoin Sulfonamides	Vancomycin Clarithromycin Chloramphenicol Fluoroquinolones Gentamicin Co-Trimoxazole	Tetracyclines Aminoglycosides (except Gentamicin)	

- **Lactation**: ***Concentration*** of an **antibiotic** in **breast milk** is ***usually*** **low**, *but* may be ***adequate*** to *cause* **serious problems** in **babies** e.g. **Quinolones** and **Sulfonamides** may cause **hemolysis** in **children** ***with*** **glucose-6-phosphate dehydrogenase** ***deficiency***.
- **Drug Allergy**: **β-lactam derivatives** and **Sulfonamides** can *cause* **allergic reactions** in ***patients with*** *history of* **allergy** to this **agents**.

4) Pharmacokinetics and Routes of Administrations;

- ***Some*** **antimicrobials**, such as **Vancomycin**, **Aminoglycosides** and **Amphotericin B** are so ***poorly*** **absorbed** *from* the **GIT** that ***adequate*** **serum levels** ***cannot*** be *obtained by* **oral administration**.

5) Antimicrobial Safety;

- **Antibiotics** *such as* **Penicillins** are among the ***least*** **toxic** of ***all*** **drugs**, while **chloramphenicol** have ***potential for*** **serious toxicity**.

6) Cost;

- ***Several*** **drugs** may **show** ***similar*** **efficacy** in **treating** an **infection** ***but*** **vary widely** in **cost**.
- **For example**; treatment of **Methicillin-resistant *Staphylococcus aureus*** (**MRSA**) generally ***includes*** **one** of the following: **Vancomycin**, **Clindamycin**, **Daptomycin** or **Linezolid**. Although ***choice of therapy*** usually centers on the;
  - **Site of infection**.
  - ***Severity*** of the **illness**.
  - ***Ability*** to **take oral medications**.
  - **Cost** of the **medication**.

Chemotherapeutic Spectra

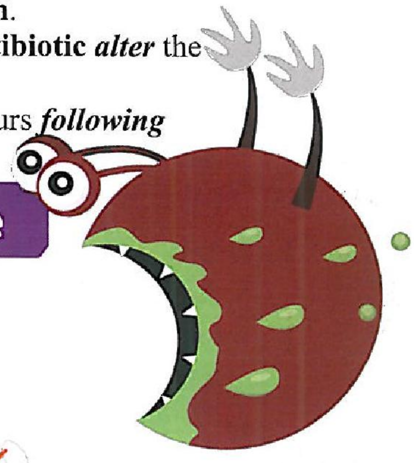
- **Narrow-spectrum;**
  - Chemotherapeutic agents *acting only* on a single or a *limited group* of microorganisms.
  - *For example*; Isoniazid is *active only* against Mycobacterium tuberculosis.
- **Extended-spectrum;**
  - Antibiotics that are *modified to* be effective *against* gram +ve and also *against* a *significant number* of gram -ve bacteria.
  - *For example*; Ampicillin or Amoxicillin is *considered to* have an extended spectrum *because* it acts *against* gram +ve and *some* gram -ve bacteria.
- **Broad-spectrum;**
  - Antibiotics that *affect* a wide variety of microbial species.
  - *For example*; Ampicillin or Amoxicillin + β-Lactamase Inhibitor, Tetracycline, Fluoroquinolones and Carbapenems.

Combination Therapy

- *Use* of **single agent** is ***more favorable due to***;
  - *Reduces* the **possibility** of **superinfections** (*see next*).
  - *Decreases resistant* of **organisms**.
  - *Minimizes* **toxicity**.
- ***However***, **some situations *require* combinations** of **antimicrobial drugs**. ***For example***, the *treatment of* **tuberculosis** *benefits from* **drug combinations**.
- **Advantage**; Synergistic effect; The *combination* is *more effective than either* of the **drugs** used **alone**.
  This can be *seen in*;
  - Co-Trimoxazole (Trimethoprim + Sulfamethoxazole)
  - Co-Amoxiclav (Amoxicillin + Clavulanic acid)
  - β-lactams + Aminoglycoside
- **Disadvantage**; Antagonism; A *number* of antibiotics *act only when* organisms are *multiplying*. *This* can be *seen in*; bacteriostatic Tetracyclines may *interfere with* the bactericidal effects of Penicillins and Cephalosporins.

Superinfection

- **Superinfection** is a *second* **infection** *superimposed* on a **first infection**.
- **Superinfection** *occur after* using **broad-spectrum antibiotic**, *this* **antibiotic** *alter* the **normal bacterial flora** and *cause* an *imbalance* of the **flora**.
- *Example*; *Overgrowth* of **endogenous *Clostridium difficile*** which occurs *following* **treatment** with a **broad-spectrum antibiotic**.



Antimicrobial Resistance

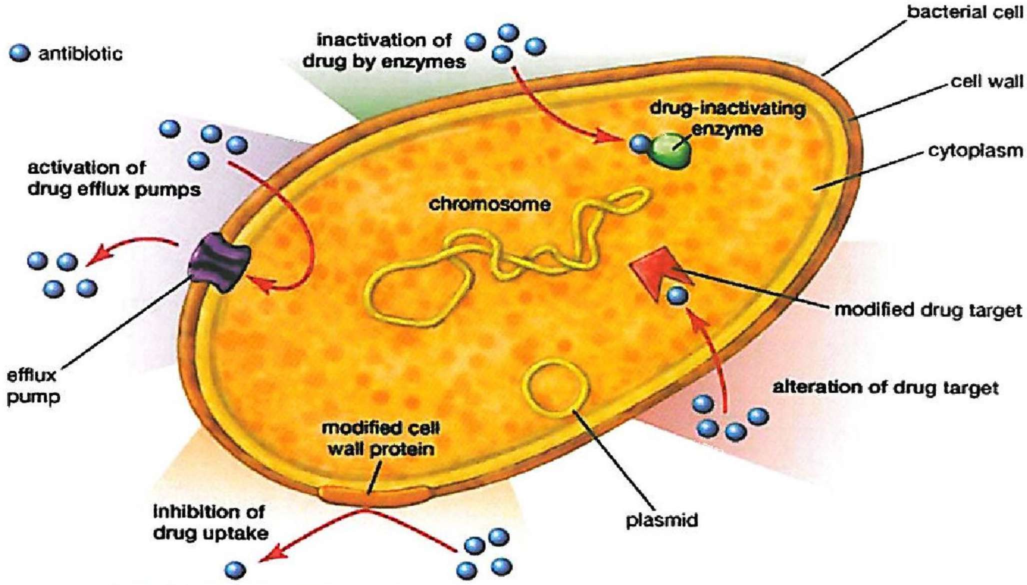
- Antimicrobial resistance is the *ability of* a microbe to *resist* the effects of antimicrobial *previously* used to *treat* them.
- Antimicrobial resistance *occurs* when microbe *change* in response to the use of *these* agent.
- Antimicrobial resistance *leads to* higher medical costs, *prolonged* hospital stays and *increased* mortality.

- The world *urgently* needs to change the *way* it prescribes and uses antimicrobial agents.
- If *new* antimicrobial agent are *developed*, *without* behaviour change, antimicrobial resistance will *remain* a *major* threat *to the* world.
- *But* the antimicrobial resistance is *rising to* dangerously high levels in *all parts* of the world.

Mechanism of Bacterial Resistance:-

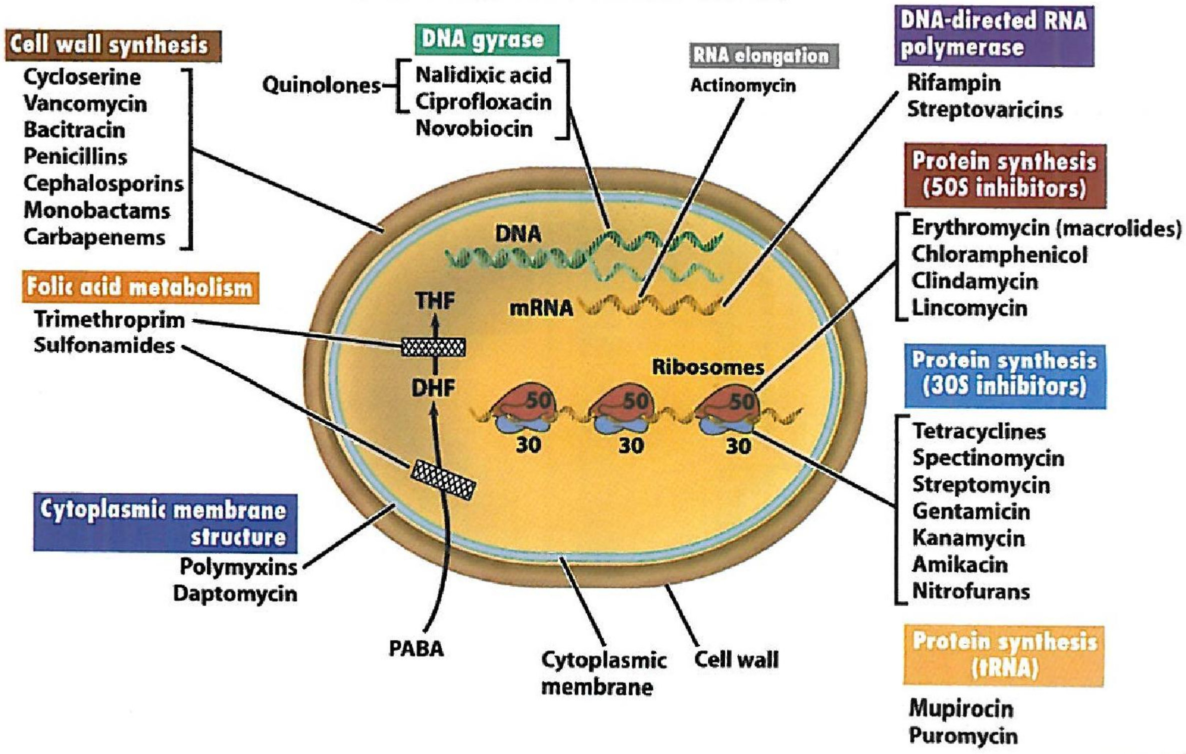
- Enzymatic inactivation; e.g. β-lactamase enzyme (Penicillinase) which *inactivate* **Penicillin** by *hydrolysis* of **β-lactam ring**.
- Impermeability to antibiotic; *Many* **antibiotics** *enter* the **cell** *through* **protein channels** called "Porin" *absence* or *mutation* or *loss* of a **porins channel** can *slow* the **rate** of drug *entry into a* **cell** or *prevent* **entry**.
- Efflux; **Bacteria** also have efflux pumps that can *transport* **drugs** *out* of the **cell**.
- Mutation; is a *change* in the **DNA** that can *sometimes cause*;
  - *Decrease* affinity of target enzyme.
  - *Alteration of* target site.
  - *Over production* of target site or metabolite.

Bacterial Resistance

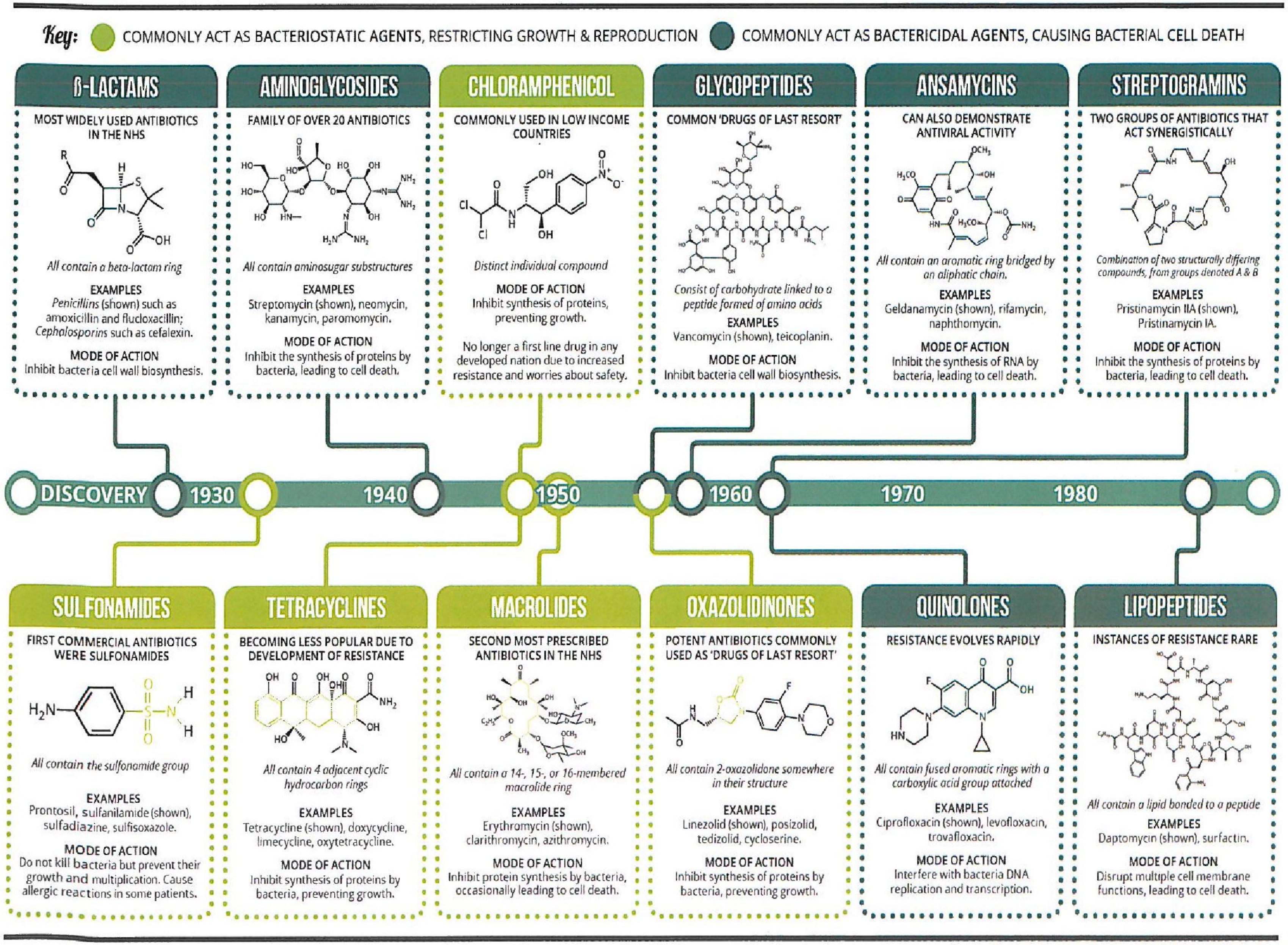

antibiotic
inactivation of drug by enzymes
bacterial cell
cell wall
drug-inactivating enzyme
cytoplasm
activation of drug efflux pumps
chromosome
modified drug target
efflux pump
alteration of drug target
modified cell wall protein
inhibition of drug uptake
plasmid

Antibiotic Classifications

(According to mechanism of action)


Cell wall synthesis
Cycloserine
Vancomycin
Bacitracin
Penicillins
Cephalosporins
Monobactams
Carbapenems
DNA gyrase
Quinolones
Nalidixic acid
Ciprofloxacin
Novobiocin
RNA elongation
Actinomycin
DNA-directed RNA polymerase
Rifampin
Streptovaricins
Protein synthesis (50S inhibitors)
Erythromycin (macrolides)
Chloramphenicol
Clindamycin
Lincomycin
Folic acid metabolism
Trimethroprim
Sulfonamides
DNA
THF
mRNA
DHF
Ribosomes
50
30
Protein synthesis (30S inhibitors)
Tetracyclines
Spectinomycin
Streptomycin
Gentamicin
Kanamycin
Amikacin
Nitrofurans
Cytoplasmic membrane structure
Polymyxins
Daptomycin
PABA
Cytoplasmic membrane
Cell wall
Protein synthesis (tRNA)
Mupirocin
Puromycin

- **Classification of Antibiotics According to Mechanism of Action:-**
  1) Agents *that inhibit* cell wall *synthesis* or *repair*.
  2) Agents *that disruption* of cell membrane *functions*.
  3) Agents *that inhibit* protein *synthesis*.
  4) Agents *that inhibit* of nucleic acid *synthesis*.
  5) Agents *that* act as antimetabolite.
- **Timeline of the Discovery of Antibiotics:-**



Key: ● COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION ● COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH

ß-LACTAMS
MOST WIDELY USED ANTIBIOTICS IN THE NHS
All contain a beta-lactam ring
EXAMPLES
Penicillins (shown) such as amoxicillin and flucloxacillin; *Cephalosporins* such as cefalexin.
MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

AMINOGLYCOSIDES
FAMILY OF OVER 20 ANTIBIOTICS
All contain aminosugar substructures
EXAMPLES
Streptomycin (shown), neomycin, kanamycin, paromomycin.
MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

CHLORAMPHENICOL
COMMONLY USED IN LOW INCOME COUNTRIES
Distinct individual compound
MODE OF ACTION
Inhibit synthesis of proteins, preventing growth.
No longer a first line drug in any developed nation due to increased resistance and worries about safety.

GLYCOPEPTIDES
COMMON 'DRUGS OF LAST RESORT'
Consist of carbohydrate linked to a peptide formed of amino acids
EXAMPLES
Vancomycin (shown), teicoplanin.
MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

ANSAMYCINS
CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY
All contain an aromatic ring bridged by an aliphatic chain.
EXAMPLES
Geldanamycin (shown), rifamycin, naphthomycin.
MODE OF ACTION
Inhibit the synthesis of RNA by bacteria, leading to cell death.

STREPTOGRAMINS
TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY
Combination of two structurally differing compounds, from groups denoted A & B
EXAMPLES
Pristinamycin IIA (shown), Pristinamycin IA.
MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

SULFONAMIDES
FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES
All contain the sulfonamide group
EXAMPLES
Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.
MODE OF ACTION
Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

TETRACYCLINES
BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE
All contain 4 adjacent cyclic hydrocarbon rings
EXAMPLES
Tetracycline (shown), doxycycline, limecycline, oxytetracycline.
MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

MACROLIDES
SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS
All contain a 14-, 15-, or 16-membered macrolide ring
EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.
MODE OF ACTION
Inhibit protein synthesis by bacteria, occasionally leading to cell death.

OXAZOLIDINONES
POTENT ANTIBIOTICS COMMONLY USED AS 'DRUGS OF LAST RESORT'
All contain 2-oxazolidone somewhere in their structure
EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.
MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

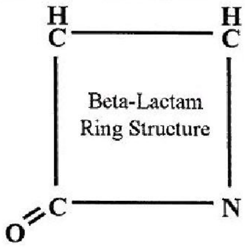
QUINOLONES
RESISTANCE EVOLVES RAPIDLY
All contain fused aromatic rings with a carboxylic acid group attached
EXAMPLES
Ciprofloxacin (shown), levofloxacin, trovafloxacin.
MODE OF ACTION
Interfere with bacteria DNA replication and transcription.

LIPOPEPTIDES
INSTANCES OF RESISTANCE RARE
All contain a lipid bonded to a peptide
EXAMPLES
Daptomycin (shown), surfactin.
MODE OF ACTION
Disrupt multiple cell membrane functions, leading to cell death.

Cell Wall Inhibitors

β-Lactams
(Similar Agents)

- **Penicillins**
- **Cephalosporins**
- **Monobactams**
- **Carbapenems**



Beta-Lactam Ring Structure

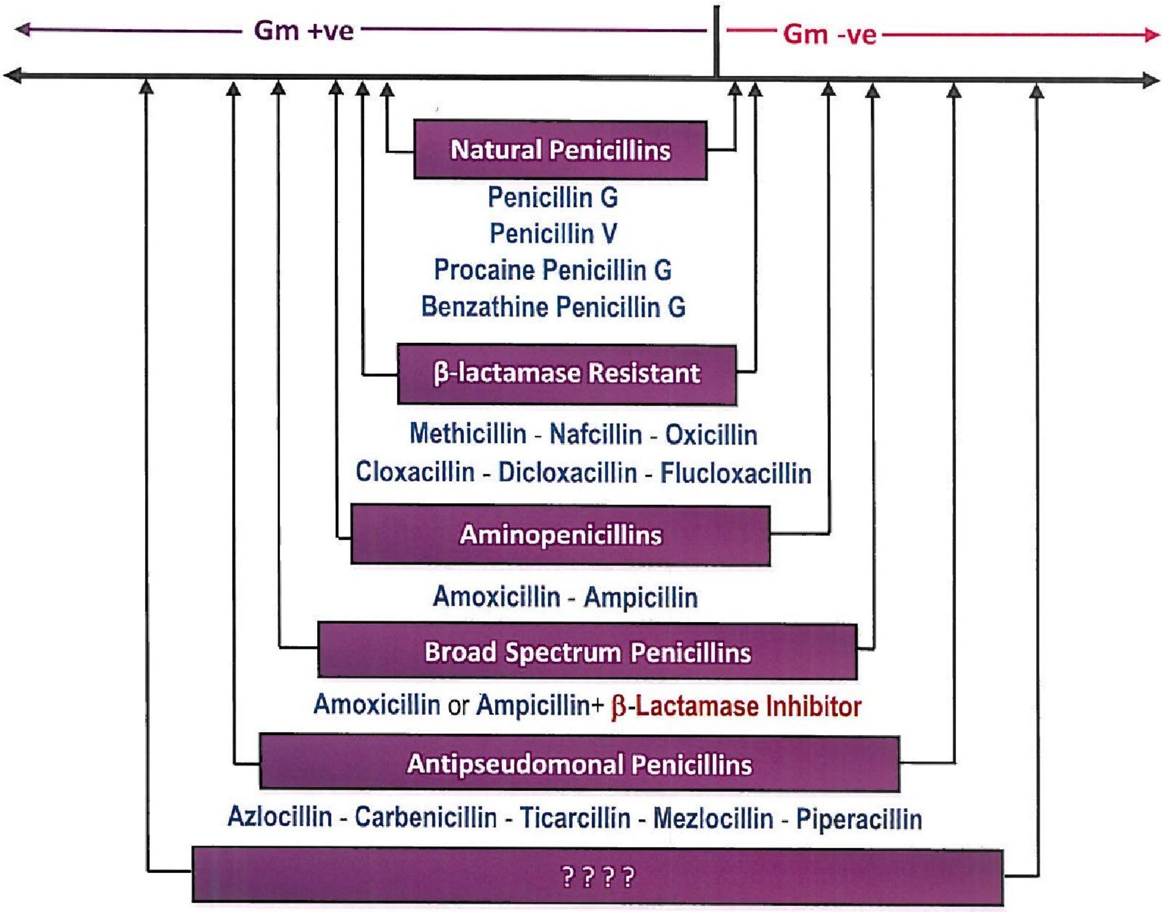
Non-β-Lactams
(Dissimilar Agents)

- **Vancomycin**
- **Fosfomycin**
- **Cycloserine**
- **Bacitracin**

A) β-Lactam Antibiotics

I) Penicillins (PCN)

➢ **Classification of Penicillins:-**



Natural Penicillins

Penicillin G
Penicillin V
Procaine Penicillin G
Benzathine Penicillin G

β-lactamase Resistant

Methicillin - Nafcillin - Oxicillin
Cloxacillin - Dicloxacillin - Flucloxacillin

Aminopenicillins

Amoxicillin - Ampicillin

Broad Spectrum Penicillins

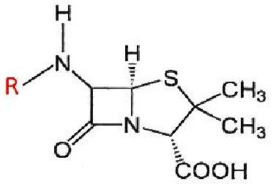
Amoxicillin or Ampicillin+ β-Lactamase Inhibitor

Antipseudomonal Penicillins

Azlocillin - Carbenicillin - Ticarcillin - Mezlocillin - Piperacillin

????

- **Penicillins** *was* **discovered** in **1928** by ***Scottish scientist*** **Alexander Fleming**.
- **Penicillin** *was* ***isolated naturally*** *from* ***Penicillium notatum*** (or ***penicillium chrysogenum***).
- **Penicillins** are the ***most widely*** **effective** and the ***least toxic*** **drugs** ***known***, but ***increased*** **resistance** has ***limited*** *their* **use**.
- There are ***several*** **enhanced Penicillins** which are ***effective against*** **additional bacteria**; include **Antistaphylococcal penicillins**, **Aminopenicillins** and the **Antipseudomonal penicillins**.
- **Penicillins** are ***derivatives*** *of* **6-AminoPenicillanic Acid (6-APA)**.



Penicillins are differ from one another in the **R** substituent attached to the **6APA** residue

Pharmaco Kinetics

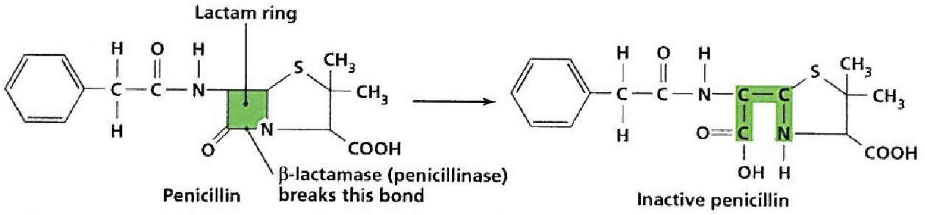
- ***Route of administration***; *determined by* the **stability** of **drug** to **gastric acid** and by the *severity* of **infection**.
- ***Absorption***; ***Most*** **oral Penicillins** (***Except***; **Amoxicillin**) is ***impaired*** by **food**, and the **drugs** ***should be*** *administered* ***at least*** **1 hour** ***before*** or **2 hours** ***after*** a **meal**.
- ***Distribution***; **distribute** ***well*** **throughout the body**.
  - ***All*** **Penicillins** ***Pass*** *easily* **placental barrier** ☞ (**Not Teratogenic**).
  - ***Penetration*** into **bone** or **cerebrospinal fluid** (**CSF**) is ***insufficient unless*** these **sites** are ***inflamed***.
  - ***Penetration*** of **Penicillins** into the **eye** and the **prostate**, is ***insufficient*** to be ***effective against*** **infections**.
- ***Excretion***; ***Primarily*** by ***active*** **tubular renal excretion**.
  - **Penicillin G** is ***rapidly*** *excreted by* the **kidneys**; *about* **30 minutes**.
  - *About* **90%** by **tubular secretion** & **10%** by **glomerular filtration**.
  - **Probenecid** ***inhibits*** **Penicillins** secretions by ***competing*** for **active tubular secretion**.
  - **Patients** with ***impaired*** **renal function** ***must*** have **dosage adjusted**.
  - **Penicillins** is also ***excreted*** *into* **sputum** and **milk** to levels **3–15%** of *those* in the **serum**.
  - **Nafcillin** is ***primarily cleared*** by **biliary excretion**.
  - **Oxacillin**, **Dicloxacillin** and **Cloxacillin** are ***eliminated*** by ***both*** the **kidney** and **biliary excretion**.

Mechanism OF Action

- **Penicillins** (and ***other*** **β-lactams**) *act by* ***binding with*** **Penicillin Binding Proteins (PBPs)** on **transpeptidase enzymes** ☞ ***Inactivation*** of **transpeptidase enzymes** (***inhibit*** **transpeptidation**) which is *responsible for* ***formation*** of **peptide bond** (***cross-linkage***) during ***formation*** or ***repair*** of **peptidoglycan** ☞ ***Decrease*** **rigidity** of **cell wall** ☞ **cell wall** ***can't*** able to ***protect*** **bacterial cell** from ***high internal*** **osmotic pressure** ☞ ***cytolysis*** ☞ **death** (**Bactericidal**).
- The ***number*** of **PBPs** varies with the **type** of **organism**. ***Alterations*** in some of these **PBPs** ***provide*** the **organism** with ***resistance*** to the **Penicillins**.

Bacterial Resistance

1) **Enzymatic inactivation**; by **β-lactamase enzyme** (**Penicillinase**).



2) ***Impermeability*** to **antibiotic** (*loss of* **Porin**).
3) **Efflux pump**; for example, ***Klebsiella pneumoniae***.
4) ***Modification of target*** **Penicillin Binding Proteins** (**PBPs**); **MRSA**.

Side Effects

1) **Hypersensitivity Reaction**; # # #
   - *About* **5%** of ***patients*** will ***develop*** a **hypersensitivity reaction**.
   - **Hypersensitivity test** ***must be*** applied at **all time** of ***injection***.
   - **Hypersensitivity test** may give ***false*** **negative result** (rare).
   - **Allergic reaction**; **Rash**, **itching** and **angioedema** (***swelling*** of the **lips**, **tongue**, and **periorbital area**).
   - **Anaphylactic shock** (***very rare***); is a ***life-threatening allergic reaction*** *include* those of an allergic reaction, as well as **bronchospasm** and ***severe*** **hypotension**.

Side Effects

- ***Anaphylaxis treatments***;
    - **Epinephrine**; **Physiologic specific antidote**.
        - One ampoule of epinephrine = 1:1000 (1 mg/1 ml).
        - If one ampoule is diluted to 10 ml = 1:10,000 (0.1 mg/1 ml).
        - **Dose in allergic reaction**;
            - IM/SC: 0.1 to 0.5 mg (0.1 to 0.5 mL of 1:1000 solution).
            - May be repeated every 10 to 15 minutes.
    - **Hydrocortisone** (**Solu-Cortef®**); *faster*.
    - **Antihistamine** ***injection***.
- **Cross-allergic reactions** *occur among* the **β-lactam antibiotics**.

2) **Super-infection**; (*Kill good bacteria in mouth and colon*).
    - **Diarrhea☞ Pseudomembranous colitis** (***Clostridium difficile***)
    - ***Treated by*** (**Vancomycin** or **Metronidazole**)
    - **Candidiasis** (oral and/or vaginal); ***Treated by*** **Nystatin** or **Miconazole**.

3) **Nephritis**;
    - **Penicillins**, ***particularly*** **Methicillin**, have the ***potential*** to cause acute **interstitial nephritis**.

4) **Neurotoxicity**;
    - ***Intrathecally*** or ***very high*** **blood levels** of **Penicillins** can ***provoke*** **seizures**.

5) **Hematologic toxicities**;
    - ***Decreased*** **coagulation** may be observed with ***high doses*** of **Piperacillin**, **Ticarcillin** and **Nafcillin**.

Natural Penicillins

- ***Natural*** **Penicillins** (**Penicillin G** and **Penicillin V**) are ***obtained from*** **fermentations** of the **fungus** ***Penicillium chrysogenum***.
- ***Semisynthetic*** **Penicillins**, such as **Amoxicillin** and **Ampicillin** (*also known as* **Aminopenicillins**).

Ultra-short Acting

Penicillin G (Benzyl-penicillin)

- **Penicillin G** [PEN-i-SIL-in G] is ***not effective*** **orally** (destroyed by gastric acidity), it is ***administrated*** **IV** or **IM** (**IV** is ***preferred*** because of irritation and local pain from IM injection of large doses), and it has ***ultra-short*** **duration of action** (half-life; about 30 minutes).
- ***2 long acting*** *forms* of **Penicillin G** are *available* for **IM injection**; **Benzathine benzylpenicillin** and **procaine benzylpenicillin**.
- ***Uses*** and ***spectrum***;
    - **Penicillin** ***remains*** the ***drug of choice*** for the treatment of **Gas Gangrene** (*Clostridium perfringens*), **Syphilis** (*Treponema pallidum*) and **Meningitis** (*Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae*).
    - **Bacterial Endocarditis** (*Staphylococcus aureus, Streptococcus viridans* and *Enterococci*)
    - **Cellulitis** (*Streptococcus* and *Staphylococcus aureus*) and **Erysipelas** (*Streptococcus*).
    - **Diphtheria** (*Corynebacterium diphtheriae*) and **Anthrax** (*Bacillus anthracis*).
    - **Actinomycosis** (*Actinomyces israelii*) (painful abscesses in the mouth, lungs, breast, or gastrointestinal tract).
    - **Tetanus** (*Clostridium tetani*); Combined with anti-toxins.
- ***Dose***; - ***Adult***; 5-24 million *units/day* IV/IM in *divided doses* every 4-6 hours.
    - ***Pediatric***; 50,000–400,000 units/kg/day in *divided doses* every 4-6 hours.

Short Acting

Penicillin V (Phenoxy-methyl-penicillin) (Ospen®) (Pen-Vee® K)

- **Penicillin V**, the ***oral form*** of **penicillin** (**Orally Penicillin**); ***more acid stable*** than **Penicillin G**.
- ***Uses*** and ***spectrum***; **Penicillin V** has a ***similar spectrum*** to that of **Penicillin G**, ***but*** is ***indicate only*** in **minor infections** ***because*** of its *relatively* **poor bioavailability** (***not used*** for **bacteremia**).
- ***Dose***; - ***Adult***; 125-500 mg every 6-8 hours.
    - ***Children***; **< 12 years**; 25-50 mg/kg/day in *divided doses* every 6-8 hours.

Intermediate Acting

Procaine Penicillin (Procaine Benzylpenicillin) or Penicillin G Procaine

- **Procaine** [PRO-kane] (***local anaesthetic***) makes the **Benzylpenicillin** ***intermediate acting***, ***following*** deep **IM injection**, it is ***slowly absorbed*** into the **circulation** and ***hydrolyzed to*** **Benzylpenicillin**, can ***last*** for ***up to*** **24 hours.**
- ***Dose***; - ***Adult***; 600,000 units to 1 million units/day IM in 1 or 2 *divided* doses.
  - ***Pediatric***; 25,000 to 50,000 units/kg/day IM in 1 or 2 *divided* doses.

Long Acting

Benzathine Penicillin (Benzathine Benzylpenicillin) or Penicillin G Benzathine

(Retarpen®) (Durapen®) (Bicillin® L-A)

- **Benzathine** [BENZ-a-theen] **Penicillin** can ***last*** for ***up to*** **3-4 weeks.**
- ***Dose***; - ***Adult***; 1.2-2.4 million unit IM as a *single dose*, in *secondary prevention every* 3-4 weeks or 600,000 units IM *every* 2 weeks.
  - ***Pediatric***; 50,000 units/kg/day IM as a *single dose* (*maximum*: 2.4 million units).
- ***Indications***; **Upper Respiratory Tract Infections**, **Rheumatic Fever Prophylaxis** and **Syphilis.**

Penicillinase-Resistant (Antistaphylococcal) Penicillins

Methicillin | **Nafcillin** | **Oxacillin** | **Cloxacillin** | **Dicloxacillin** | **Flucloxacillin**

- **Antistaphylococcal penicillins** are ***semisynthetic*** **penicillins** with **β-lactamase (penicillinase)-resistant.**
- Their use is ***restricted*** to the **treatment** *of* ***infections*** caused by **Methicillin Sensitive *Staphylococcus aureus*** (**MSSA**).
- In ***recent years*** the **empirical use** of these drugs has ***decreased*** *substantially* ***because*** of ***increasing*** **rates** of **Methicillin-Resistance *Staphylococcus aureus*** (**MRSA**).
- **MRSA** is ***currently*** a ***source of*** **serious infections** and is ***resistant*** to ***most commercially*** *available* **β-lactam antibiotics.**
- **Methicillin** [meth-i-SILL-in] is ***not*** **absorbed** ***orally***, ***only*** **given** by **IV route** and has a ***higher*** **frequency** of **interstitial nephritis.**
- **Nafcillin** [naf-SILL-in] has ***poor*** **oral absorption** and is **given** by **IV** or **IM routes**, it is ***used for staphylococcal*** **endocarditis.**
- **Oxacillin** [ox-a-SILL-in], **Cloxacillin** [kloks-a-SILL-in], **Dicloxacillin** [dye-klox-a-SILL-in] and **Flucloxacillin** [floo-klox-a-SILL-in] can be ***administered*** **orally.**
- ***Common combinations with*** **Aminopenicillins**;
  - **Cloxacillin** 250 mg + **Ampicillin** 250 mg; Ampiclox® 500 mg
  - **Dicloxacillin** 250 mg + **Ampicillin** 250 mg; Cloxapen® 500 mg
  - **Flucloxacillin** 125/250/500 mg + **Amoxicillin** 125/250/500 mg; Flumox® 250/500/1000 mg

Aminopenicillins

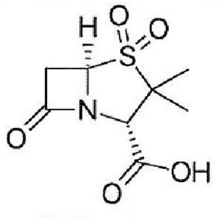
Ampicillin | **Amoxicillin**

- ***Unlike*** the **natural penicillins**, ***these agents*** exhibit ***increased*** **stability** to **gastric acid hydrolysis.**
- **Ampicillin** [am-pi-SILL-in] and **Amoxicillin** [a-mox-i-SILL-in] have an **antibacterial spectrum** ***similar*** to that of **Penicillin G** but are ***more effective*** *against* **Gram -ve bacilli bacilli** (enhanced ability to penetrate the gram-negative outer membrane).
- ***Bioavailability*** of **Amoxicillin** is ***greater than*** **Ampicillin** (***oral*** **Ampicillin** has been ***favored for*** treatment of a localized ***Shigella*** infection).
- ***Absorption*** of **Ampicillin** is ***impaired*** by **food**, and the drugs ***should be*** administered ***at least*** **1 hour** ***before*** or **2 hours** ***after*** **a meal.**
- **Bacampicillin** is a ***prodrug*** of **Ampicillin** to ***increase*** **absorption.**
- **Ampicillin** (***with*** or ***without*** **Gentamicin**) is the ***drug of choice*** for ***Listeria monocytogenes.***
- **Ampicillin** and **Amoxicillin** are ***excreted*** **unchanged** in the **urine.**
- ***Doses***; - ***Adult***; **250-500 mg *orally*** (**Ampicillin** ***every*** **6 hours** - **Amoxicillin** ***every*** **8 hours**).
  - **Ampicillin**; **500 mg** to **2 g IM/IV *every* 6 hours.**
  - ***Pediatric***; **25-50 mg /kg/day** in; **Amoxicillin 3 *divided* doses**, **Ampicillin 4 *divided* doses.**
- ***Most common side effects***; **Diarrhea** ☞ **Pseudomembranous colitis** (*clostridium difficile*).

Broad Spectrum Penicillins (Aminopenicillins + β-lactamase Enzyme Inhibitors)

Ampicillin/Sulbactam (Unasyn®) | **Sultamicillin** (Unasyn® Oral)

Co-Amoxiclav (Amoxicillin/Clavulanate) (Augmentin®)


Sulbactam

- **Sulbactam** [sul-BAK-tam], **Clavulanate** [KLAV-yoo-la-nate] (**Clavulanic acid**), **Tazobactam** [TAZ-oh-BAK-tam] and **Avibactam** [a-vi-BAK-tam] are **β-lactamase enzyme *inhibitors*.**
- **β-lactamase enzyme *inhibitors*** are ***similar*** in **chemical structure** of **β-lactam antibiotics** *allows* to ***interact with*** the **β-lactamase enzyme *secreted by*** *certain* **bacteria** that ***resistance*** to **β-lactam antibiotics** and ***irreversible inhibits*** **β-lactamase enzyme.**
- **Sultamicillin**; is a ***prodrug*** ***oral*** ***form*** of the ***antibiotic combination*** **Ampicillin/Sulbactam *results in*** **2.5 times *greater concentration*** of **Ampicillin** and **Sulbactam** than when ***given*** **alone.**
- ***Indications***; - **Otitis Media** and **Sinusitis.**
  - **Respiratory Tract Infections.**
  - **Skin and Skin Structure Infections.**
  - **Urinary Tract Infections** (caused by beta-lactamase–producing *E. coli*, *Klebsiella* species).
- ***Doses***; **A) Amoxicillin/Clavulanate (Co-Amoxiclav)**;
  - ***Adult***; **500 mg (Augmentin® 625)** ***orally*** *every* **8 hours** or **875 mg (Augmentin® 1 gm)** ***orally*** *every* **12 hours.** ***Children* < 40 kg**; **45 mg/kg/day** ***divided doses every*** **12 hours.**
  - ***Extend-release formulations***;
    - **Augmentin® ES-600; 600 mg Amoxicillin /42.9 Clavulanic acid** in ***5 mL***;
      - **90 mg/kg/day** for **10 days** in ***recurrent*** or ***persistent acute*** **otitis media.**
    - **Augmentin® XR; 1000 mg Amoxicillin /62.5 Clavulanic acid** in **1** ***tablet***;
      - **≤ 16 years; 2 tabs** ***every*** **12 hrs** in **community acquired pneumonia, acute exacerbations of chronic bronchitis** and **acute bacterial sinusitis**; for 7-10 days.

  B) Ampicillin/Sulbactam;
  - ***Adult***; **1.5** to **3 g IV** or **IM** ***every*** **6 hours** (**Sulbactam *not exceed*** **4 g** *per* **day**).
  - ***Children* < 40 kg**; **300 mg/kg/day** ***divided doses every*** **6 hours** (**300 mg** ***represents*** the ***total*** **Ampicillin + Sulbactam**).
  - ***After reconstitution***; use ***within*** **2 hours** if ***stored*** at **room temperature**, or within **4 hours** if ***stored*** *under* **refrigeration.**

  C) Sultamicillin (Unasyn® 375 or **750)**; ***Adults***; is **375-750 mg** ***orally*** **twice daily.**
- ***Most common side effects***; **Diarrhea☞ Pseudomembranous colitis** (*clostridium difficile*).

Anti-Pseudomonal Penicillins

Carboxypenicillins

Ticarcillin | **Carbenicillin**

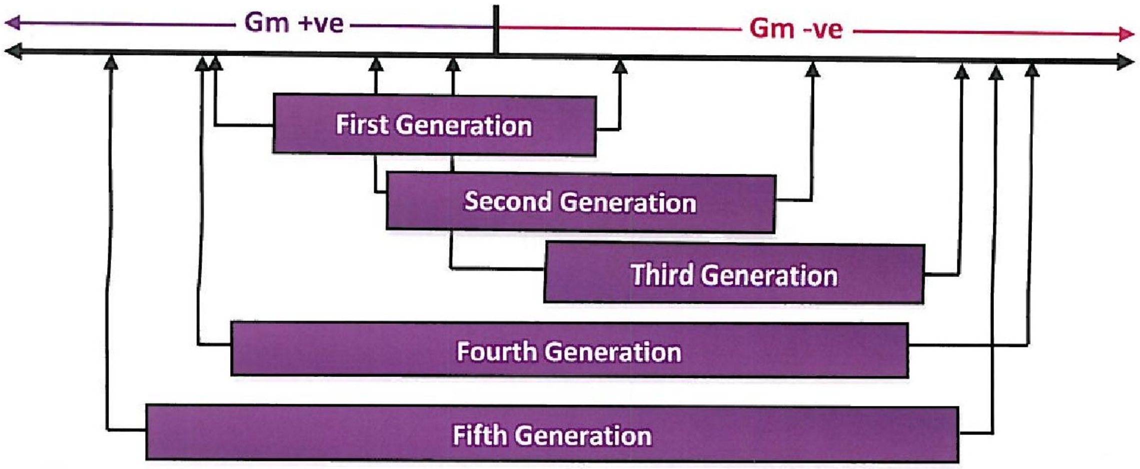
Ureidopenicillins

Piperacillin | **Mezlocillin** | **Azlocillin**

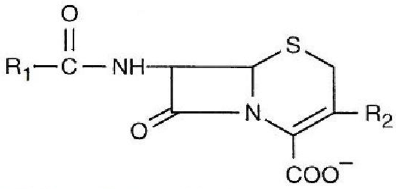
- **Ticarcillin** [TYE-kar-SIL-in], **Carbenicillin** [kar-ben-i-SIL-in], **Piperacillin** [PI-per-a-SIL-in], **Mezlocillin** [ME-z-loo-SIL-in] and **Azlocillin** [AZ-loo-SIL-in] are ***developed to further increase*** *activity* ***against*** **Gm -ve resistant aerobes**, *especially* ***Pseudomonas aeruginosa.***
- **Piperacillin** is the ***most potent*** of these **antibiotics. Carbenicillin** is the ***only*** **orally** ***available.***
- ***Formulation*** of **Ticarcillin + Clavulanic acid** (Timentin®) and **Piperacillin + Tazobactam** (Tazocin®) are ***available*** and *widely* **used** and have **good** *activity* ***against*** **penicillinase-producing organisms** (for example, most ***Enterobacteriaceae*** and ***Bacteroides*** **species**).
- ***Doses***; - **Ticarcillin + Clavulanic acid** (Timentin®); - ***Adult***; **≥ 60 kg; 3.1 g IV** ***every*** **4-6 hours.**
  - ***Children* < 60 kg** and **> 3 months**; **200-300 mg/kg/day IV** ***divided doses every*** **4-6 hours.**
  - **Piperacillin + Tazobactam** (Tazocin®); - ***Adult***; **3.375 g IV** ***every*** **4-6 hours.**
    - ***Children* < 40 kg**; **80-100 mg/kg IV** ***every*** **4-6 hours.**

II) Cephalosporins

➢ Classification of Cephalosporins:-



- 1st **generation** are ***active predominantly*** *against* **Gram +ve bacteria**, and ***successive generations increased activity*** *against* **Gram -ve bacteria**.
- 2nd **generation**; *has* **effect** on **Gram +ve** (***less than*** 1st **generation**) and ***some*** of **Gram -ve**.
- 3rd **generation**; *has* **high effect** on **Gram -ve**.
- 4th **generation**; *has* **high effect** on **Gram -ve** and **Gram +ve**.



Cephalosporins are ***differ from one another*** R_1 and R_2 ***substituent attached*** to **7-ACA**

- **Cephalosporins** are **β-lactam antibiotics** that are ***closely related*** both ***structurally*** and ***functionally*** to the **Penicillins**.
- **Cephalosporins** were ***discovered*** in **1945** by the *Italian pharmacologist* **Giuseppe Brotzu** and were ***first sold*** in **1964**.
- **Cephalosporins** ***was isolated naturally*** *from* ***Cephalosporium acremonium*** and are ***derivatives*** *of* **7-Amino-Cephalosporanic Acid (7-ACA)**.
- **Cephalosporins** have the ***same*** **mode of action** as **Penicillins**, and they are affected by the ***same*** **resistance mechanisms**.
- ***All*** **Cephalosporins** are ***ineffective*** **against MRSA** (**5th generation** are ***active*** **against MRSA** and **VRSA**) ***Listeria monocytogenes***, ***Clostridium difficile*** and **enterococci** (***Enterococcus faecalis*** and ***Enterococcus faecium***).

Pharmaco Kinetics

- ***All*** **cephalosporins distribute** ***very well into*** **body fluids**.
- ***All*** **cephalosporins** ***cross*** the **placenta**.
- **Cephalosporins** are ***eliminated*** through **tubular secretion** and/or **glomerular filtration**; ***Need*** **dose adjustment** in **renal dysfunction** (*Except*; **Ceftriaxone** and **Cefoperazone** which is *excreted through* the **bile** into the **feces**).

Side Effects

- ***Like*** **Penicillins**; **Cephalosporins** are ***most widely effective*** and the ***least toxic*** **drugs** *known*.
- **Allergic reactions** (**cross-sensitivity**);
  - *About* **1%** *of patients* with a *history of* **Penicillin *allergy*** will have an ***allergic reaction*** if given a **Cephalosporin**.
  - **Cephalosporin *should be* avoided** or *used with* **caution** (***especially*** **first-generation cephalosporins**) in individuals with **Penicillin *allergy***.
- ***Mild*** **stomach cramps** or **upset nausea**, **vomiting** and **diarrhea**.
- **Superinfection** (***as*** **Penicillins**).
- **Interstitial Nephritis**.
- ***Some*** **Cephalosporins** are *associated with* **Hypoprothrombinemia** and a **disulfiram-like reaction** *with* **Ethanol** (N-methylthiotetrazole side-chain of these cephalosporins, blocks vitamin K epoxide reductase enzyme such as **Cefoperazone**).

First Generation Cephalosporins

Cefadroxil (Duricef®) | **Cephalaxin** (Keflex®) | **Cephradine** (Velosef®)

Cefazolin (Zinol®)

***Good* activity *against* Gram +ve**	***Staphylococcus aureus*** ***Staphylococcus epidermidis*** ***Streptococcus pyogenes*** ***Streptococcus pneumoniae*** **Anaerobic streptococci**	★★
***Some* activity *against* Gram -ve**	***Escherichia coli*** ***Klebsiella pneumoniae*** ***Proteus mirabilis***	★

- **Cefadroxil** [SEFF-ah-DROX-il], **Cephalaxin** [sef-a-LEX-in] and **Cephradine** [SEF-ra-deen] and **Cefazolin** [sef-A-zoe-lin] are the ***most common*** **1st generation cephalosporins.**
- **Cefazolin** is ***available only*** in ***parenteral*** **formulation.**
- **This group *not* cross** the **blood-brain barrier (BBB)** ⇨ ***Not effective*** in **Meningitis.**
- ***Doses***;

Agent	Usual Adult Dose	Usual Children Dose
Cefadroxil	500-1000 mg orally every 12 hours	30 mg/kg/day orally divided every 12 hours
Cephalaxin	250-1000 mg orally every 6 hours	25-50 mg/kg/day orally divided every 6-8 hours
Cephradine	250-500 mg orally every 6 hours 500-1000 mg orally every 12 hours	25-50 mg/kg/day divided every 6-12 hours
Cefazolin	500-1000 mg IV every 6-8 hours	25-100 mg/kg/day IV/IM divided every 6-8 hours

Second Generation Cephalosporins

Cefaclor (Ceclor®) | **Cefuroxime** (Zinacef®)

Cefprozil (Cefzil®) | **Cefoxitin** (Mefoxin®)

***Some* activity *against* Gram +ve**	***Staphylococcus aureus*** ***Streptococcus pyogenes*** ***Streptococcus pneumoniae*** **Anaerobic streptococci**	★
***Good* activity *against* Gram -ve**	**Same as 1st generation** ***Haemophilus influenza*** ***Enterobacter aerogenes*** ***Neisseria* spp.**	★★

- **Cefaclor** [SEFF-uh-klor], **Cefuroxime** [SEF-ue-ROX-eem], **Cefprozil** [sef-PROE-zil] and **Cefoxitin** [sef-OX-i-tin] are the ***most common*** **2nd generation cephalosporins.**
- **This group *not* cross** the **BBB** ***except*** **Cefuroxime** (*less effective* than **Ceftriaxone** or **Cefotaxime**).
- ***Orally*** **Cefuroxime** is ***not acceptable taste need to*** **shaking** for **long time** to **decrease *it*.**
- **Cephamycins**; **Cefotetan**, **Cefoxitin** and **Cefmetazole** are ***only*** **cephalosporins** have ***moderate*** **activity *against* anaerobes** (like; ***Bacteroides fragilis***).
- ***Doses***;

Agent	Usual Adult Dose	Usual Children Dose
Cefaclor	250-500 mg orally every 8 hours	20-40 mg/kg/day orally divided every 8 hours
Cefuroxime	250-500mg orally every 12 hours 500-750 mg IV every 8 hours	30 mg/kg/day orally divided every 12 hours 75-150 mg/kg/day IV/IM divided every 8 hours
Cefprozil	250-500 mg orally every 12 hours	15-30 mg/kg/day divided every 12 hours
Cefoxitin	1-2 g IV every 6-8 hours	80-160 mg/kg/day IV divided every 4-6 hours

Third Generation Cephalosporins

Parenteral	
Ceftriaxone (Rocephin®)	**Cefotaxime** (Claforan®)
Cefoperazone (Cefobid®)	**Ceftazidime** (Fortum®)
Oral	
Cefixime (Suprax®)	**Cefdinir** (Omnicef®)
Cefpodoxime (Orelox®)	**Cefditoren** (Meiact®)

Less activity *against* Gram +ve	***Streptococcus pneumoniae*** ***Streptococcus pyogenes*** **Anaerobic streptococci**
Excellent activity *against* Gram -ve	**Same as 2nd generation** ***Pseudomonas aeruginosa*** ***Serratia marcescens*** ★★★

- **Ceftriaxone** [SEF-trye-AX-one], **Cefotaxime** [SEF-oh-TAX-eem], **Cefoperazone** [sef-oh-PER-a-zone] and **Ceftazidime** [sef-TAZ-i-deem] are the ***most common*** **parenteral 3rd generation cephalosporins** and are **able** to *cross* the **BBB**.
- **Cefixime** [sef-IX-eem], **Cefdinir** [SEF-di-nir], **Cefpodoxime** [SEF-poe-DOX-eem] and **Cefditoren** [SEF-di-TOR-en] are the ***most common*** **oral 3rd generation cephalosporins.**
- **This group** *have* a **broad spectrum** of *activity* and *further increased* **activity** *against* **gram -ve.**
- **Ceftazidime** and **Cefoperazone** are the ***only two drugs have*** **antipseudomonal activity.**
- **Cefoperazone 1000 mg** are available in combination with **Sulbactam 500 mg**; **Sulperazon®**
- **Cefoperazone** may ***cause*** **testicular atrophy** in **animals**, ***not*** **widely *used*** in **children.**
- **Ceftriaxone** are **soluble** in **Lidocaine** and ***available*** in **IM** ***parenteral*** **formulations** (**IM ONLY**; to ***avoid*** **systemic toxicity** of **Lidocaine**).
- **DON'T MIX Ceftriaxone** with a **Calcium-containing product** (**Ringer's solution**).
- **Ceftriaxone NOT used** in **premature neonates** & **hyperbilirubinemic neonates**; ***displace*** **Bilirubin.**
- The ***excretion*** of **Cefoperazone** and **Ceftriaxone** is ***mainly*** through the **biliary** tract, and ***no dosage*** **adjustment** is ***required*** in **renal insufficiency**.
- **This group** are the ***drug of choice*** in ☞ **Typhoid fever**, **Gonorrhoea** and **Meningitis** (**Ceftriaxone** and **Cefotaxime**).
- ***Common indications***;
  - **Otitis Media**
  - **Skin and Skin Structure Infections**
  - **Urinary Tract Infections**
  - **Bone and Joint Infections**
  - **Surgical Prophylaxis**
  - **Pharyngitis** and **Tonsillitis**
  - **Respiratory Tract Infections**
  - **Bacterial Septicemia**
  - **Intra-abdominal Infections**
- ***Doses***;

Agent	Usual Adult Dose	Usual Children Dose
Ceftriaxone	1-2 g/day IV/IM in single daily dose or divided every 12 hours	50-75 mg/kg IV/IM in single daily dose or divided every 12 hours
Cefotaxime	1-2 g IV every 8 hours	50-200 mg/kg/day IV/IM divided every 8 hours
Cefoperazone	2-4 g/day IV/IM divided every 12 h	100-150mg/kg/day IV/IM divided every 8-12h
Ceftazidime	500 mg-2 g IV/IM every 8-12 hours	30-50 mg/kg IV every 8-12 hours
Cefixime	400 mg/day orally in single daily dose or divided every 12 hours	8 mg/kg/day orally in single daily dose or divided every 12 hours (weight X 0.4 = mL)
Cefdinir	600 mg/day orally in single daily dose or divided every 12 hours	14 mg/kg/day orally in single daily dose or divided every 12 hours
Cefpodoxime	100-400 mg orally every 12 hours	5 mg/kg (max. 200 mg) orally every 12 hours
Cefditoren	*Approved only* for; ≥ 12 years; 200-400 mg orally every 12 hours	

- **Ceftazidime/Avibactam** (**Avycaz®**); It was ***approved*** in **2015** for ***Complicated*** **Intra-Abdominal Infections (cIAIs)** and ***Complicated*** **Urinary Tract Infections (cUTIs)**. **Avibactam** is a ***novel*** **non-β-lactam β-lactamase inhibitor.**

Fourth Generation Cephalosporins

Cefepime (Maxipime®)

Cefpirome (Cefrom®)

- **Cefepime** [SEF-e-peem] and **Cefpirome** [SEF-pir-ome] are **4th generation cephalosporins.**

★★★★

- **This group** ***have*** an ***excellent*** **activity** ***against*** **Gram -ve** and **Gram +ve.**
- **This group** ***have*** **good activity** ***against Pseudomonas aeruginosa, Staphylococcus aureus***, and ***multiple drug-resistant Streptococcus pneumoniae.***
- **Cefepime** is ***used*** in;
  - **Pneumonia**
  - ***Empiric*** **treatment of febrile neutropenic patients**
  - ***Uncomplicated*** **and** ***Complicated*** **Urinary Tract Infections**
  - ***Uncomplicated*** **Skin** and **Skin Structure Infections (uSSSIs).**
  - ***Complicated*** **Intra-abdominal Infections** (***in combination*** with **Metronidazole**).
  - **Brain abscess**
- ***Doses***; **Cefepime**;- ***Adult***; 1-2 g IV every 8-12 hours - ***Children***; 50 mg/kg IV every 12 hours
  Cefpirome;- ***Adult***; 1-4 g IV every 12 hours - ***Children***; Not recommended
- Febrile neutropenia is the development of fever, often with other signs of infection, in a patient with neutropenia.

Fifth Generation Cephalosporins

Ceftobiprole (Zevtera®)

Ceftaroline (Teflaro®)

Ceftolozane (Zerbaxa®)

- **Ceftobiprole** [sef-TO-beep-role], **Ceftaroline** [sef-TAR-oh-leen] and **Ceftolozane** [sef-TOL-oh-zane] are **5th generation cephalosporins.**

★★★★★

- **This group** are ***developed for*** the **treatment** of ***infections*** with **gram -ve** and **gram +ve bacteria** that have ***become*** **resistant** to ***conventional*** **antibiotics.**
- **They are** ***active against***; - **Methicillin-resistant *Staphylococcus aureus* (MRSA).**
  - **Vancomycin-resistant *Staphylococcus aureus* (VRSA).**
- **Ceftobiprole** and **Ceftaroline** are the ***active moiety*** of the ***prodrug*** **Ceftobiprole medocaril** and **Ceftaroline fosamil.**
- **Ceftolozane** is ***combined with*** the **β-lactamase inhibitor Tazobactam.**
- ***Indications***;
  - **Ceftobiprole**; - ***Hospital*-Acquired Pneumonia (HAP).**
    - ***Community*-Acquired Pneumonia (CAP).**
  - **Ceftaroline fosamil**; - ***Community*-Acquired Pneumonia (CAP).**
    - ***Complicated*** **Skin and Skin Structure Infections (cSSSIs).**
  - **Ceftolozane/Tazobactam**; - ***Complicated*** **Urinary Tract Infections (cUTIs).**
    - ***Complicated*** **Intra-Abdominal Infections (cIAIs).**

III) Monobactams

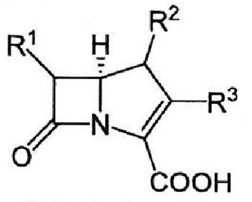
- **Monobactams** are ***β-lactam antibiotics*** wherein the **β-lactam ring** is ***alone*** (***monocyclic*** **β-lactam**) and ***not fused*** to ***another*** **ring**, in *contrast to most other* **β-lactams.**

Aztreonam (Azactam®)

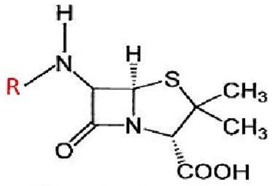
- **Aztreonam** [az-TREE-oh-nam], is the ***only commercially available*** **monobactam.**
- It has ***antimicrobial activity*** **primarily** ***against*** **Gram -ve**, *including* ***Enterobacteriaceae*** and ***Pseudomonas aeruginosa*** (***similar to*** that **3rd generation cephalosporins**).
- It ***lacks activity against*** **Gram +ve** or **anaerobes.**
- ***Administration***; **IV** or **IM** and can ***accumulate*** in **patients with renal dysfunction.**
- It ***penetrates*** **well** ***into*** the **cerebrospinal fluid.**
- It ***used*** to treat ***serious infections*** such as **pneumonia, meningitis,** and **sepsis** caused by ***susceptible*** **Gram -ve** in ***patients with*** **hypersensitivity to penicillins (NO cross-hypersensitivity).**
- ***Dose***; - ***Adult***; 1-2 g IV/IM *every* 8-12 hours. - ***Children***; 30 mg/kg IV *every* 8 hours.
- ***Nebulized forms*** of **Aztreonam (Cayston®)** is ***approved*** for **cystic fibrosis.**

IV) Carbapenems

- **Carbapenems** are *structurally related* to **β-lactam antibiotics**.
- **Carbapenems** *differ in* **structure** *from* the **Penicillins** in that the **sulfur atom** of the **thiazolidine ring**.
- They *exhibit* a **broader spectrum** of *activity compared to* **Cephalosporins** and **Penicillins**.
- **Carbapenems** were *originally developed* from the **Thienamycin**, a *naturally derived* product of *Streptomyces cattleya*.



Core structure of the Carbapenem molecules



Core structure of the Penicillins

- **Carbapenems** in *general* have **seizure risk** in *high* **doses**.
- *Most common* **side effects** (*more common* with **Imipenem**); **nausea, vomiting, diarrhea, skin rashes,** and **infusion site reactions.**
- *Renal failure*; **Doses** ***must*** be *adjusted* (*may lead* to **seizures**); **Meropenem**, **Doripenem**, and **Ertapenem** are *much less* **likely** to *cause* **seizures** *than* **Imipenem**.

Imipenem/Cilastatin (Tienam®)

- **Imipenem** [IM-i-PEN-em] is the *first drug* of this **class**, *discovered by* **Merck** in the *mid*-**1970s**.
- **Imipenem** is *compounded with* **Cilastatin** [SYE-la-STAT-in] to *protect it* from **metabolism** by **renal dehydropeptidase**;
  - **Imipenem** is *rapidly* ***degraded by*** the **Dehydropeptidase** (**Dipeptides**) *renal enzyme* when **administered** *alone* (**Nephrotoxic Metabolite**).
  - *Co-administered* with **Cilastatin** (**Dehydropeptidase** *enzyme inhibitors*) ⇨ ***Prevent*** this *inactivation* (*prevents* **formation** of **toxic metabolite** and *increase* **urinary concentration**).
- **Imipenem/Cilastatin** is *administered* **IV** and *penetrate well* into **body tissues** and **fluids**, *including* the **CSF** in *inflamed* **meninges**.
- *Spectrum of activity*; **aerobic** and **anaerobic**, **Gram +ve** and **Gram -ve** *including* ***Pseudomonas***.
- It *indicated for*; **Pneumonia, sepsis, endocarditis, joint infections, intra-abdominal infections,** and **urinary tract infections.**
- *Dose*; - *Adult* (≥70 kg); **IV**; 250-1000 mg *every* 6-8 hours.
  - *Pediatric* (*for non-CNS infections*); 25 mg/kg IV; *every* 12 hours in age less than 7 days.
    every 8 hours in age 1 to 4 weeks.
    every 6 hours in age 4 weeks to 3 months.
    15-25 mg/kg IV; *every* 6 hours in age 3 months or older.

Meropenem (Meronem®)	**Doripenem** (Doribax®)
Ertapenem (Invanz®)	**Tebipenem** (Orapenem®)

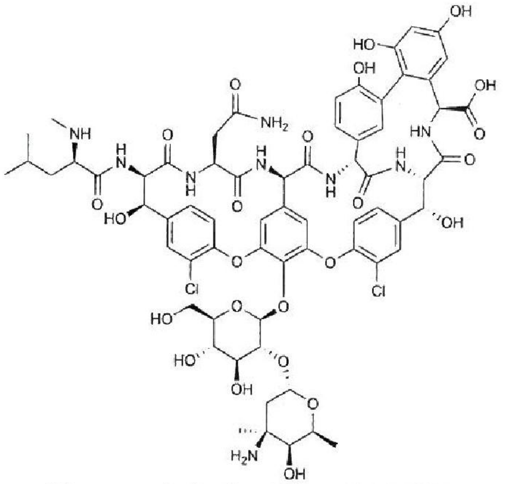
- **Meropenem** [MER-oh-PEN-em], **Doripenem** [DOR-i-PEN-em], **Ertapenem** [ER-ta-PEN-em] and **Tebipenem** [TEEP-i-PEN-em] are **Carbapenems**;
  - **UN-LIKE Imipenem**; **NOT** *metabolized by* **dehydropeptidase**.
  - **LIKE Imipenem**; **SAME** *spectrum of* **activity** (***Except*** **Ertapenem** is ***not*** **active *against*;** ***Pseudomonas***, ***Acinetobacter*** and **Enterococci**).
- **Tebipenem**; is the *first* **oral carbapenem** whose *prodrug only marketed* in **Japan**.
- They are *indicated for*; - *Complicated* **Skin and Skin Structure Infections (cSSSIs).**
  - *Complicated* **Intra-Abdominal Infections (cIAIs).**
  - *Community*-**Acquired Pneumonia (CAP).**
  - *Complicated* **Urinary Tract Infections (cUTIs).**
  - **Febrile Neutropenia.** - **Acute Pelvic Infections.**
- **Meropenem** 1g/**Vaborbactam** 1g (**Vabomere®**) is **US FDA approved** in **Aug, 2017** for **adults** *with complicated* **urinary tract infections (cUTIs).**
- *Doses*;

Agent	Usual Adult Dose	Usual Children Dose
Meropenem	500-1000 mg IV *every* 8 hours	≥ 3 months; 10-40 mg/kg IV *every* 8 hours
Ertapenem	> 13 years; 1 g IV/IM *per* day	3 months-13 years; 15 mg/kg IV/IM *twice* daily.
Doripenem	Only for ≥18 years; 500 mg IV infusion *over* 1 hour *every* 8 hours	

B) Non-β-lactam Cell Wall Inhibitors

I) Glycopeptide Antibiotics

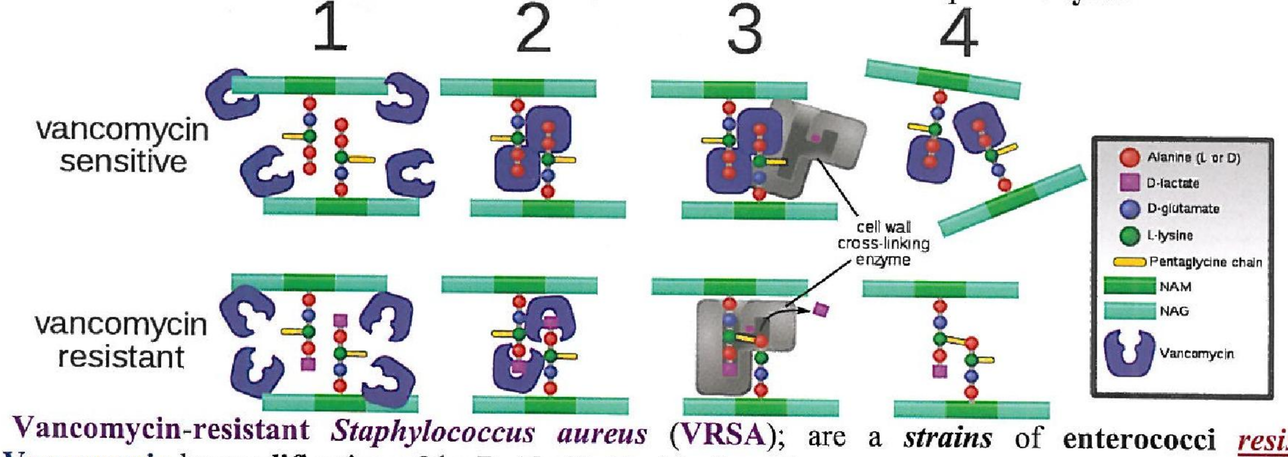
- **Glycopeptide antibiotics** are ***composed*** of ***glycosylated*** *cyclic* or *polycyclic* **non-ribosomal peptides**.
- **Glycopeptide antibiotics** such as **Vancomycin**, **Teicoplanin**, **Telavancin** and **Bleomycin**.
- ***Administration***; *Due to* ***large*** **chemical structure** and ***high*** **molecular weight** of this **group** they are ***poorly*** **absorbed orally**, and ***available*** as ***parenteral*** **formulations** for ***systemic*** **infections** and are ***effective*** **principally** ***against*** **Gram +ve** ***cocci*** (***poorly*** **penetrate Gram -ve** ***phospholipid*** **membrane**).
- ***Lipophilic*** **side-chains** *linked to* **Glycopeptides** are ***developed*** such as **Telavancin**.
- **Bleomycin** used to ***treat*** **cancer**.



Vancomycin (molecular weight 1500)

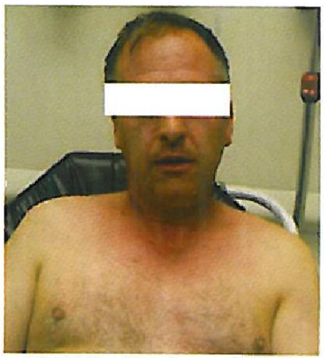
Vancomycin

- **Vancomycin** [VAN-koe-MYE-sin] is an antibiotic ***produced by*** *Streptococcus orientalis* and *Amycolatopsis orientalis* and was ***first isolated*** in **1953**.
- It is ***active only against*** **Gram +ve bacteria**; **NOT effective** ***against*** **Gram -ve**; ***poorly*** **penetrate phospholipid membrane**.
- **Vancomycin** is ***not absorbed*** after **oral** ***administration***.
- **FIRST-LINE** ***for***;
  1) **IV**; ***complicated*** **skin infections, bacteraemia, endocarditis, bone and joint infections, and meningitis** ***caused by*** **Methicillin-resistant** ***Staphylococcus aureus*** **(MRSA)** and **Methicillin-resistant** ***Staphylococcus epidermidis*** **(MRSE)**.
  2) **Oral**; **Pseudomembranous colitis** ***caused by Clostridium difficile*** (**Oral capsules**; ***not absorbed*** and **Vancomycin** ***act*** **locally**).
- ***Mechanism of action***; **Vancomycin** ***inhibits*** **cell wall synthesis** by ***binding*** firmly to the **D-alanyl-D-alanine** (D-Ala-D-Ala) in ***peptidoglycan***, ***preventing*** *further* **elongation** of ***peptidoglycan*** and ***cross-linking***. The **peptidoglycan** is thus ***weakened***, and the **cell** *becomes* susceptible to **lysis**.



- **Vancomycin-resistant** ***Staphylococcus aureus*** **(VRSA)**; are a ***strains*** of **enterococci** ***resist*** **Vancomycin** by ***modification of*** the **D-Ala-D-Ala** ***binding*** **site**.
- ***Dose***; - **IV Infusion**; 15-20 mg/kg/*every* 8-12 hr (In a dilute solution slowly, over at least 60 min.).
  - Dosage is reduced in patients with renal insufficiency.
  - **Oral**; 125 mg orally *every* 6 hours for10 day {Powder for injection can be used to prepare oral capsules or solution for oral administration if not available or expensive}.
  - **Inhalation** (*off-label*); via nebulizer, for treatment of various infections of the upper and lower respiratory; 250 mg (5 mL from diluted vials) twice daily by nebulization.

- ***Side Effects***;
    - **Red Man Syndrome** (**RMS**) or **Red Neck**; *infusion reaction*
        - *Usually* **appearing** *rapidly after* **infusion.**
        - *Non-specific* **mast cell degranulation** → *release* of **Histamine** → ***Redness*** and ***hotness*** in **face** and **neck.**
        - *Treatments*; *decrease* **infusion rate** and use **emollients, topical steroids, antihistamines & antibiotics** (for secondary infection).
        - *Prophylaxis*; *prolonging* **infusion period** to **1–2 hours** and *pre-treatment* with an **antihistamine** such as **Diphenhydramine.**
    - **Nephrotoxicity** and **Ototoxicity**; *increases* the **toxicity** of ***other*** **nephrotoxins** or **ototoxins** such as **Aminoglycosides.**



Red Man Syndrome (RMS)

Teicoplanin (Targocid®)

- **Teicoplanin** [tye-koe-PLAN-in] is a ***semi-synthetic derivative*** of **Vancomycin** that is ***very similar*** to **Vancomycin** in ***mechanism*** and ***spectrum***.
- ***Unlike*** **Vancomycin**, it can be given **IM** or **IV** and has a ***long*** **half-life** (45–70 hrs); ***once-daily*** **dosing.**

Telavancin (Vibativ®)

- **Telavancin** [tel-a-VAN-sin] is ***semi-synthetic*** **lipoglycopeptide** ***derivative*** of **Vancomycin.**
- ***Spectrum***; **Telavancin** is *active against* **Gram +ve bacteria**, ***including*** **strains** with ***reduced*** **susceptibility** to **Vancomycin.**
- ***Mechanism***; ***Like*** **Vancomycin**, **Telavancin** ***inhibits*** **bacterial cell wall synthesis** by ***binding*** to the **D-Ala-D-Ala** *terminus* of the **peptidoglycan** in the *growing* **cell wall.** ***In addition***, it *disrupts* **bacterial** ***cell membranes*** by **depolarization** (***similar to*** that of **Daptomycin**).
- ***Half-life***; *about* **8 hours,** *which* **supports once-daily IV dosing.**
- **Telavancin** is approved in 2009 for ***complicated*** **Skin and Skin Structure Infections** (**cSSSIs**) and in 2013 for ***hospital-acquired*** **pneumonia** *caused by* ***Staphylococcus aureus***.
- ***Monitoring***; ***Unlike*** **Vancomycin** ***therapy***, ***monitoring*** of serum **Telavancin** *levels* is ***not required***.
- ***Pregnancy***; **Telavancin** is ***potentially*** **teratogenic**, and **pregnancy test** *must be* **confirmed** (**Vancomycin** is **FDA** ***category*** **B**).

Dalbavancin (Dalvance®) (Xydalba®)

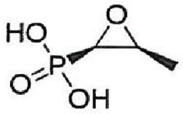
Oritavancin (Orbactiv®)

- **Dalbavancin** [dal-ba-VAN-sin] and **Oritavancin** [or-IT-a-VAN-sin] are a ***novel*** **second-generation** ***semisynthetic*** **lipoglycopeptide.**
- ***Spectrum***; ***Improved*** **activity** ***against*** many **Gram +ve bacteria** ***including*** **MRSA**, ***Streptococcus pyogenes***, ***Streptococcus agalactiae*** and ***Streptococcus anginosus*** group.
- ***Mechanism***; ***Like*** **Vancomycin.**
- ***Half-life***; *about* **6-11 days,** *which* **supports once-weekly IV dosing** (***single dose***).
- **Dalbavancin** and **Oritavancin** was ***approved*** in **2014** for ***acute*** **bacterial skin** and **skin structure infections** (**ABSSSIs**) in ***adults***.
- **Oritavancin** ***inhibits*** **Warfarin** ***metabolism***.

II) Others

Fosfomycin

Fosfomycin (Monuril®) (Monurol®)



- **Fosfomycin** [fos-foe-MYE-sin] (**Phosphomycin** or **Phosphonomycin**) is a ***broad-spectrum antibiotic*** (***against*** many **Gram +ve** and **Gram –ve**)
- **Fosfomycin** is ***indicated*** in the ***treatment*** of **urinary tract infections** (**UTIs**), as a ***single*** **oral megadose**.
- ***Mechanism***; It ***blocks*** **cell wall synthesis** by ***inhibiting*** **UDP-N-acetylglucosamine enolpyruvyl transferase** ***enzyme***, *which catalyzes* the ***first step*** in **peptidoglycan synthesis**.
- ***Dose***; - ***Single*** **3 g dose** *for* ***uncomplicated*** **lower urinary tract infections**.
  - **3 g** *every* **2** to **3 days** ***for*** **3 doses** *for* ***complicated*** **urinary tract infections** (*off-label*).
  - **3 g** *every* **3 days** ***for*** **21 days** *for* **prostatitis** (*off-label*).
- ***Pregnancy***; ***FDA category*** **B**.
- **Parenteral** ***formulation*** is *available* in ***some*** **countries** for **systemic infections**.

Bacitracin

Bacitracin

- **Bacitracin** [bass-ih-TRAY-sin] is a ***cyclic peptide*** **mixture** (**polypeptide**) ***first*** obtained from *Bacillus subtilis* in **1943**.
- ***Spectrum***; ***active against*** **Gram +ve bacteria** (***high*** **molecular weight**; ***poorly*** **penetrate Gram -ve** ***phospholipid*** **membrane** and ***poorly*** **absorbed**).
- ***Mechanism***; **Bacitracin** ***inhibits*** **cell wall** ***synthesis*** by ***interfering*** with ***dephosphorylation*** in **cycling** of the **lipid carrier** that ***transfers*** **peptidoglycan** ***subunits*** to the **growing cell wall**.
- **Bacitracin** is ***highly*** **nephrotoxic** when ***administered*** **systemically** and is **ONLY** ***used*** **topically**.
- It is often ***combined with*** **Polymyxin** or **Neomycin** and ***may cause*** **allergy**.
- ***Solutions*** of **Bacitracin** in **saline** can be ***used for*** **irrigation** in **wounds**.

Cycloserine

Cycloserine (Seromycin®)

- **Cycloserine** [sigh-kloe-SER-een] is an ***antibiotic*** was ***discovered in*** **1954** from a type of *Streptomyces*.
- ***Spectrum***; **Cycloserine** ***inhibits many*** **Gram +ve** and **Gram -ve bacteria**, ***but*** it is ***used*** **ONLY** as a ***second line*** in treat **tuberculosis**.
- ***Mechanism***; **Cycloserine** is a ***structural analog*** of **D-alanine** and ***inhibits*** the **incorporation** of **D-alanine** ***into*** **peptidoglycan pentapeptide**.
- **Cycloserine** is ***widely*** **distributed** in **tissues**.
- **Cycloserine** causes ***serious*** **dose-related CNS toxicity**; **headaches**, **tremors**, ***acute*** **psychosis** and **convulsions**.

Teixobactin

Teixobactin

- **Teixobactin** is a ***new*** **antibiotic** (not approved yet; 2/2018) of a ***new class*** with a ***novel*** **mechanism** of **action** by ***inhibiting*** **peptidoglycan** ***biosynthesis via binding*** to **lipid II**, a ***precursor*** to **peptidoglycan**.
- ***Spectrum***; ***active against*** **Gram +ve bacteria** (*Staphylococcus aureus* or *Mycobacterium tuberculosis*).
- **Teixobactin** was ***discovered*** **using** a ***new*** **method** of ***culturing*** **bacteria** in **soil**.

Arylomycins

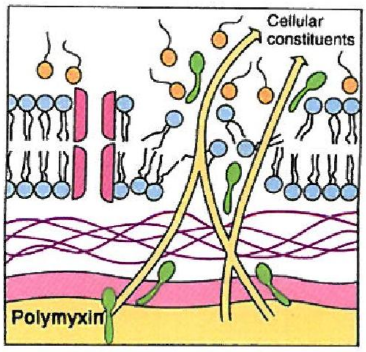
- **Arylomycins** are a ***new*** **class** of **Gram-negative antibiotics** may have ***applications*** in ***treating*** **multidrug-resistant Gram -ve bacterial infections** and they have therefore attracted research interest.
- Synesthetic analogs of Arylomycins, such as G0775, have been developed which have broader spectrum activity and greater efficacy.

Cell Membrane Disruption Antibiotics

Polypeptide

Polymyxin B

Polymyxin E (Colistin)

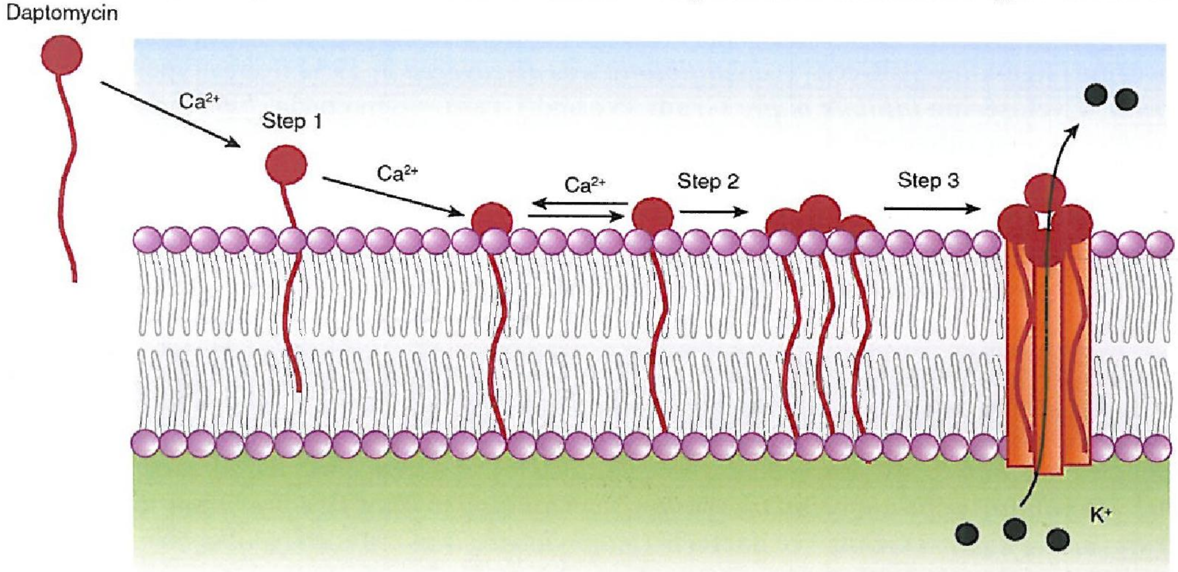


- ***Mechanism***; **Polymyxins** are **cation$^+$** ***polypeptides*** that ***bind*** to **phospholipids$^-$** on ***bacterial*** **cell membrane** and ***disrupts*** **cell membrane** of **Gram -ve bacteria** (**detergent-*like* effect**), *leading to* ***leakage of*** **cellular components** and ***ultimately*** **cell death**.
- ***Spectrum***; **Polymyxins** ***inhibit many*** **important Gram -ve bacteria**; including ***Pseudomonas aeruginosa***, ***Escherichia coli***, ***Klebsiella pneumoniae***, ***Acinetobacter*** species, and ***Enterobacter*** species.
- **Polymyxins** are ***relatively*** **neurotoxic** and **nephrotoxic**, so are usually ***used*** **ONLY** as a ***last*** resort in ***treating*** **infections** ***caused by*** **multiple drug-resistant bacteria**.
- ***Only*** **2 forms** of **Polymyxins** are ***available*** in ***clinical used***;
  - **Polymyxin B**; *available as* **parenteral**, **ophthalmic** and **topical** ***preparations***.
  - **Polymyxin E** (**Colistin**); *available as* a **prodrug**, **Colistimethate sodium**, which is ***administered*** **IV** or **inhaled** via a **nebulizer**.

Lipopeptide

Daptomycin (Cubicin®)

- **Daptomycin** [DAP-toe-MYE-sin] is a ***novel*** **cyclic lipopeptide** ***fermentation product*** of *Streptomyces roseosporus*. It was discovered by Eli Lilly and Company in the late **1980s**.
- It is ***used*** in the *treatment of* ***systemic*** and ***life-threatening*** **infections** caused by **Gram +ve bacteria**.
- ***Spectrum***; ***Similar to*** **Vancomycin**, ***but more rapidly*** **bactericidal** and ***active against*** **Vancomycin-resistant** strains of ***enterococci*** (**VRE**) and ***Streptococcus aureus*** (**VRSA**).
- ***Mechanism***; **Daptomycin** ***binds*** to **cell membrane** *via* **calcium-dependent** ***insertion*** of its **lipid tail**. ***This results*** in ***depolarization*** of the **cell membrane** with ***potassium*** **efflux** and ***rapid*** **cell death**.



- It is ***indicated for***; for ***systemic*** and ***life-threatening*** **infections** *caused by* **Gram +ve**;
  - ***Complicated*** **Skin and Skin Structure Infections** (**cSSSIs**).
  - ***Staphylococcus aureus*** **Bacteraemia**.
  - ***Staphylococcus aureus*** **Endocarditis**.
- ***Dose***; 4-6 mg/kg IV *every* 24 hours.
- Daptomycin is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia.
- **Myopathy** and **rhabdomyolysis** have been ***reported*** in patients *simultaneously* taking **statins**; thereby **statins** ***should be*** *temporarily* ***discontinued*** while the patient is receiving **Daptomycin** ***therapy***.

Protein Synthesis Inhibitors

Tetracyclines
- Tetracycline
- Oxytetracycline
- Demeclocycline
- Minocycline
- Doxycycline

Glycylcyclines

Aminoglycosides
- Streptomycin
- Neomycin
- Gentamicin
- Amikacin
- Tobramycin

Macrolides
- Erythromycin
- Clarithromycin
- Azithromycin
- Roxithromycin
- Spiramycin

Ketolides

Chloramphenicol

Oxazolidinones

Lincosamides

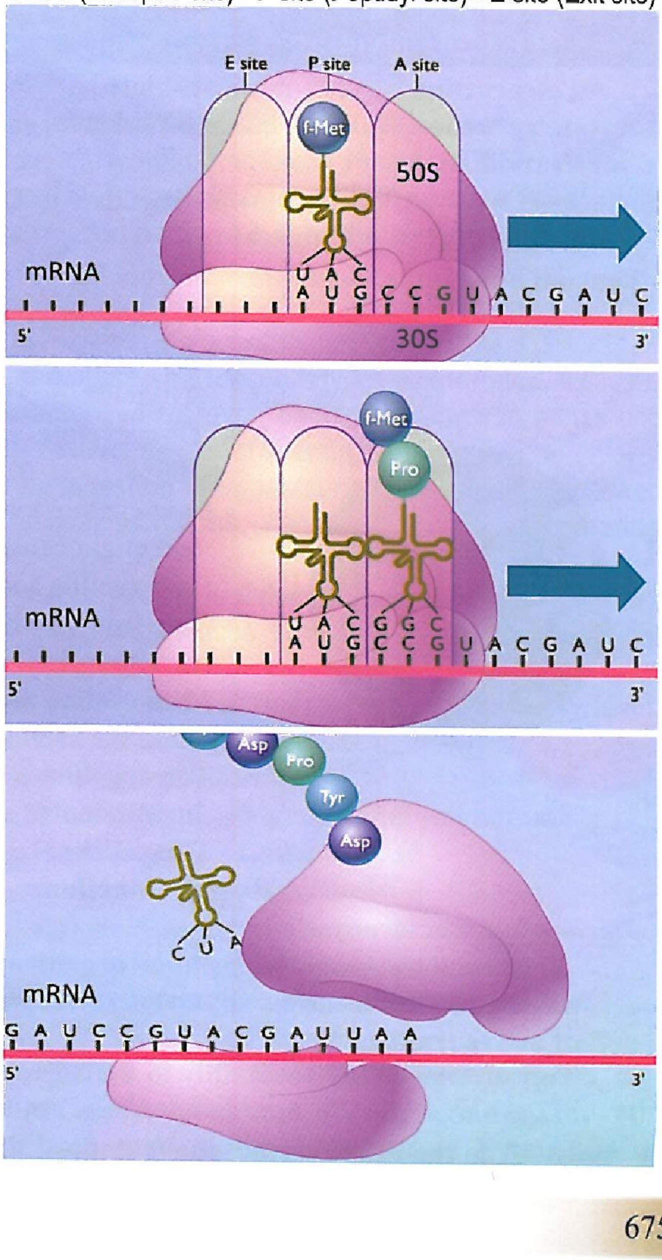
Streptogramins

Others

➢ Bacterial Protein Synthesis:-

- **Bacterial cell** (**Prokaryotic**) have a **70S** *ribosome* (**50S** ***large*** **subunit** and **30S** ***small*** **subunit**), but **human cell** (**Eukaryotic**) have a **80S** *ribosome* (**60S** ***large*** **subunit** and **40S** ***small*** **subunit**).
- **Prokaryotic** and **Eukaryotic** have a ***different structure*** to **ribosomes** so can use **antibiotics** for *selective* **toxicity** *against* **ribosomes** of **prokaryotes**.
- ***Bacterial Protein Synthesis Steps***;

A site (**A**cceptor site) - **P** site (**P**eptidyl site) - **E** site (**E**xit site)



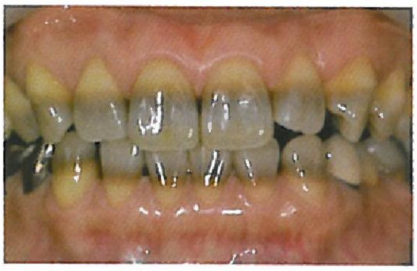
1) ***Initiation***;
   - ***Initiate*** **formation** of **70S ribosome** *from* **30S** and **50S**.
   - ***Required*** **initiation** (*start*) **codon** (**AUG**) and **initiation factor** (**IF**).
   - **AUG** ***corresponds*** to **N-formyl-methionine** ***amino acid***.
2) ***Elongation***;
   - By ***formation*** of **peptide bond** ***between*** **amino acids**.
   - ***Required*** **peptidyl transferase** ***enzyme*** and **elongation factor** (**EF**).
3) ***Translocation*** or ***Propagation***;
   - ***Movement*** of the **ribosome** through **mRNA**.
4) ***Termination***;
   - It ***required*** **termination** ***non-sense codon*** (**UAA - UAG - UGA**) and **release factors** (**RF**).

- ***Protein Synthesis Inhibitors***;
  - **30S** ***subunit reversible*** *binding*;
    * **Tetracyclines** (**Bacteriostatic**)
  - **30S** ***subunit irreversible*** *binding*;
    * **Aminoglycosides** (**Bactericidal**)*
  - **50S** ***subunit reversible*** *binding*;
    * **Chloramphenicol** (**Bacteriostatic**)
  - **50S** ***subunit irreversible*** *binding*;
    * **Macrolides** & **Clindamycin** (**Bacteriostatic**)

- ***Doses***;
  - **Tetracycline**; - **Adult**; 500 mg orally *every* 6 hours
    - **Children**; > 8 years; 25-50 mg/kg/day divided in 4 doses
  - **Demeclocycline**; - **Adult**; 600-1200 mg/day orally divided *every* 3 to 4 doses
    - **Children**; > 8 years;7-13 mg/kg/day orally divided in 2 to 4 doses
  - **Doxycycline**; * **Oral or IV infusion**;
    - **Adult**; - ***Initial***; *Oral*; 200 mg in 2 divided doses in the first day.
      IV Infusion; 200 mg in 1 or 2 divided doses in the first day.
      - ***Maintenance***; *Oral*; 100 mg orally once a day OR 50 mg orally every 12 hours.
        IV Infusion; 100 to 200 mg/day IV infusion.
    - **Children**; - ***Initial***; > 8 years; 4.4 mg/kg *orally/IV* on the first day, in 2 divided doses.
      - ***Maintenance***; > 8 years; 2.2 mg/kg *orally/IV* once a day OR 1.1 mg/kg twice.
  - **Minocycline**; * **Oral or IV infusion**;
    - **Adult**; 200 mg initially followed by 100 mg every 12 hours.
    - **Children**; > 8 years: 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Side Effects

- **GIT discomfort** (*local irritation*); **Esophageal irritation**, **anorexia**, **nausea**, **vomiting** and **diarrhea** (**esophagitis** may be ***minimized*** by ***coadministration*** with **food** [***except*** **Tetracycline**] or **fluids** with ***standing up*** *if possible* and **use capsule *products***).
- **Calcified tissues**; **Discoloration** and **hypoplasia** of **teeth** and ***effect*** on **bone growth** in ***children less than*** **8 years** and **fetus *during* pregnancy** (**Teratogenic**; **Category D**).



- **Vestibular disturbance**; **Dizziness**, **vertigo** and **tinnitus** *particularly* with **Minocycline**.
- **Photosensitivity**; ***Severe*** **sunburn *may occur*** and ***more frequently*** with **Tetracycline** and **Demeclocycline**.
- **Hepatotoxicity**; ***rare***, ***but*** **fatal**; may occur ***with*** **high IV doses**, ***particularly*** in **pregnancy** or **patients hepatic** or **renal *dysfunction***.
- **Renal Toxicity** (***except*** **Doxycycline**); **Acidosis** and **azotaemia** (high level of nitrogen in the blood); ***particularly*** in **patients *with* impaired kidney function**.
- **Fanconi syndrome**; Results by ***ingesting expired*** **Tetracyclines**; *converted to* **4-Epitetracycline** and **Anhydrotetracycline** which ***damage*** **proximal tubule**.
- **Pseudotumor cerebri**; ***rare***; ***benign***, **intracranial hypertension** (**headache** and **blurred vision**) *may occur*.

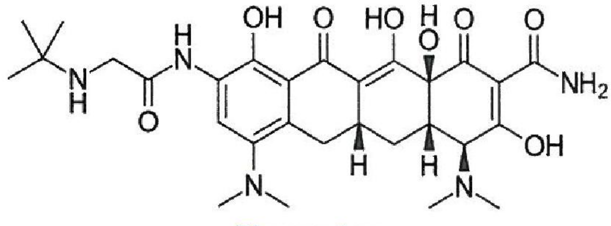
- ***Contraindications***; - **Children *less than* 8 year**.
  - **Pregnancy** (**Teratogenic**; **Category D**).

*** Tetracyclines Precautions ***

Patient Counselling

1) ***Taken*** *with* **food** (***except*** **Tetracycline**), *with* ***large*** **amount** of **water** and ***remain*** **upright** *if possible*, and ***choose*** **capsule products**.
2) ***Don't take*** with **calcium-rich foods** as; **milk & milk products**.
3) ***Don't take*** with ***other drugs*** *specially*; **Ca**, **Iron** and **Antacids**.
4) ***Don't used*** for **children *less than* 8 years** and **pregnancy**.
5) ***Avoid*** **sun exposure** OR ***Use*** **sun screen**.
6) ***Need*** **dose adjustment** in **kidney/liver failure** (***except*** **Doxycycline**).
7) **Check *for* expiry date**.

Glycylcyclines



Tigecycline

(by adding a bulky N,N-dimethyl**glycyl**amido side chain to position 9 of **Minocycline**)

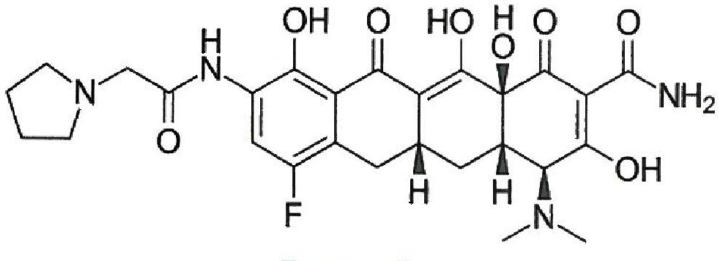
- **Glycylcyclines** are a ***new class*** of **antibiotics** ***derived from*** **Tetracyclines**.
- **Glycylcyclines** are *specifically* ***designed to*** *overcome* **2** ***common*** **mechanisms** of **Tetracyclines** ***resistance***;
    - **1) Efflux pumps** and/or
    - **2) Ribosomal protection**.
- **Tigecycline** is the ***only*** **glycylcycline** *approved for* **antibiotic use**.

Tigecycline (Tygacil®)

- **Tigecycline** [TYE-ge-SYE-kleen] is the ***first*** and ***only*** **glycylcycline** ***available***, it is a ***derivative of*** **Minocycline** and *marketed by* **Pfizer** *under* the ***brand name*** **Tygacil®**. It was **FDA** ***approved*** in **2005**.
- ***Mechanism***; **LIKE Tetracyclines**, ***but*** **bind** ***more*** **effectively** ***than*** the **Tetracyclines**.
- ***Spectrum***;
    - **Broad-spectrum activity** ***including*** those of **multi-drug resistance**; **Methicillin-resistant** ***Staphylococcus aureus*** **(MRSA)**, **Vancomycin-resistant** **strains** of ***enterococci*** **(VRE)**, **β-lactamase–*producing*** **Gram -ve bacteria** and ***many*** **anaerobic organisms**.
    - ***Not*** **active against**; ***Proteus***, ***Providencia*** or ***Pseudomonas*** **species** (due to; it contains **chromosomal efflux pumps**).
- ***Indications***;
    - ***Complicated*** **Skin and Skin Structure Infections (cSSSIs)**.
    - ***Complicated*** **Intra-Abdominal Infections (cIAIs)**.
    - ***Community*-Acquired Pneumonia (CAP)**.
- ***Dose***;
    - ***Adult***; > 17 years; 100 mg IV infusion *initial dose*, *followed by* 50 mg IV *every* 12 hours.
    - ***Pediatric***; - 8 *to* 11 years; 1.2 mg/kg IV infusion *every* 12 hours.
        - 12 *to* 17 years; 50 mg IV infusion *every* 12 hours.
- **Tigecycline** ***primary*** **excreted** *via* **biliary/faecal** (**No** **dose adjustments** in ***patients with*** **renal impairment**), ***However***, a ***dose reduction*** is ***recommended*** in ***severe*** **hepatic dysfunction**.
- ***Black box warning***; **Tigecycline** ***should be*** **reserved** ***for*** **use** in **situations** ***when*** **alternative treatments** are ***not*** **suitable**; ***increased*** **mortality**.
- **Tigecycline** may also ***have potential*** for **use** in **acute myeloid leukemia**.
- ***Side effects***; **LIKE Tetracyclines**.
- **Tigecycline** may ***decrease*** the **clearance** of **Warfarin** and ***increase*** **prothrombin time**.

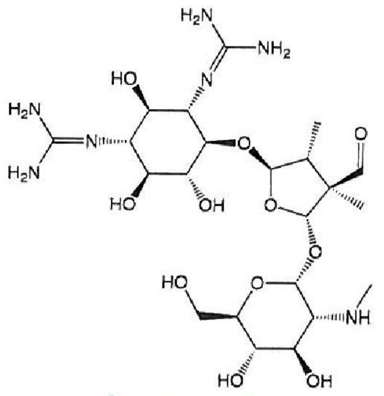
Fluorocyclines

- **Fluorocyclines** are a ***new class*** of **antibiotics** ***closely related*** to the **Tetracyclines** and **Glycylcyclines**.
- **Fluorocyclines** are ***developed by*** **Tetraphase Pharmaceuticals**.
- **Eravacycline** (Xerava®) is the ***first*** and ***only*** **drug** in ***this*** **class**. It is ***approved*** **in 27/8/2018** for ***complicated*** **Intra-Abdominal Infections (cIAIs)** in **adults age 18 years** and ***older***.



Eravacycline

Aminoglycosides



Streptomycin

- The term "**Aminoglycoside**" stems from ***their structure***; ***two*** or ***more* amino sugars *joined by*** a **glycosidic *linkage*** to a ***central* hexose *nucleus***.
- **Aminoglycosides** are ***derived from*** either ***Streptomyces* sp.** (have **−mycin** suffixes) or ***Micromonospora* sp.** (have **−micin** suffixes).
- **Aminoglycosides** are **used *most widely*** in ***combination*** with a **β-lactams** in ***serious infections*** with **Gram -ve bacteria**, in ***combination*** with **Vancomycin** or a **β-lactams** for **Gram +ve endocarditis**, and for ***treatment*** of **tuberculosis**.
- The ***first member*** of the group to be ***discovered*** is **Streptomycin** in **1943** *by* **Albert Schatz**, in the *laboratory of* **Selman Waksman** and funded *by* **Merck** and **Co.** from *Streptomyces griseus.* It was the ***first antibiotic*** cure for **Tuberculosis (TB)**.

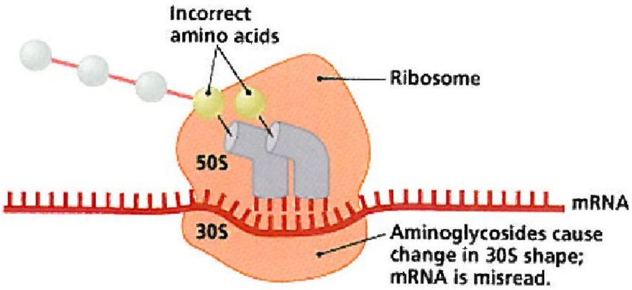
Streptomycin	**Neomycin**	**Amikacin** (Amikin®)
Gentamicin (Garamycin®)	**Tobramycin** (Tobrex®)	

- **Streptomycin** [strep-toe-MYE-sin], **Neomycin** [nee-oh-MYEsin], **Amikacin** [am-i-KAY-sin], **Gentamicin** [jen-ta-MYE-sin] and **Tobramycin** [toe-bra-MYE-sin] are the ***most common*** **Aminoglycosides**.

Pharmaco Kinetics

- ***Absorption***; ***absorbed very* poorly** *from* **GIT** (*due to* **polycationic structure**), and ***almost*** the ***entire* oral dose** is ***excreted*** in **feces** ***after*** **oral administration**.
- ***Administrations***;
  - ***All* Aminoglycosides** (***except*** **Neomycin**; *due to severe* **nephrotoxicity**) ***must be given*** **parenterally (IM** or **IV *infusion*)**.
  - ***Oral* Aminoglycosides** such as **Neomycin** can be ***used for*** **preoperative bowel preparation** and for **hepatic encephalopathy** or **hepatic coma**.
  - ***Topical* Aminoglycosides** can be ***used for*** **skin/eye infections**.
- ***Distribution***;
  - **Aminoglycosides** are ***highly* polar compounds** that ***do not*** *enter* **cells** *readily*.
  - ***Concentrations*** in **CSF** are ***inadequate***, even in the ***presence*** of ***inflamed*** **meninges**.
  - ***All* Aminoglycosides *cross*** the **placental barrier**.
- ***Once-Daily Dosing***;
  - **Aminoglycosides** have a ***narrow therapeutic index*** and **therapeutic drug monitoring (TDM)** is ***necessary*** to ***obtain*** the **correct dose**.
  - **Aminoglycosides** have ***concentration-dependent killing*** (**spectrum** and **bactericidal effect** ***depending on*** *their* **concentration**).
  - They ***also*** have a ***significant*** **post-antibiotic effect** (***continued*** **suppression** of **bacterial growth** ***after removal*** of this **agent** *from* the **environment**; ***due to strong, irreversible*** **binding** to the **ribosome**).
  - ***Once-daily dosing***; ***more*** **effective**, ***more*** **convenient**, and ***safer*** **dosing regimen** ***than*** **2** or **3 *equally divided*** **doses**.
  - ***Once-daily dosing*** is ***generally avoided*** in ***patients with severe*** **renal impairment**.
- ***Excretion***: ***More than* 90%** of the ***parenteral*** **aminoglycosides** are ***excreted*** **unchanged** in the **urine**. ***Dose adjustments*** are ***required*** in in ***patients with*** **renal impairment**.

- *Mechanism*; Bactericidal (concentration *dependent*);
  - **Aminoglycosides** *enter susceptible* **organisms** by **passive diffusion** *via* **porin channels**, and then *actively* **transported** *across* the **cell membrane** *into* the **cytoplasm** by an **oxygen-dependent process**; **Anaerobic bacteria** *such as Bacteroides fragilis* are *innately* **resistant**.
  - **Aminoglycosides** *bind* **irreversibly** to the **30S** *subunit interfere* with **assembly** of the *functional* **ribosomal apparatus** and *cause misreading* of **mRNA**, which *causes incorporation* of *incorrect* **amino acids** into the **peptide** and *results in* a **non-functional** or **toxic protein**.
  - **Aminoglycosides** are *unique* in that they are **bactericidal** (**Protein synthesis inhibitors** are *generally* **bacteriostatic**).



Bacterial Resistance

1) Enzymatic inactivation; *production* of a **transferase enzyme** or **enzymes** *inactivates* the **Aminoglycoside** by *adenylylation*, *acetylation*, or *phosphorylation* (**Amikacin** is *less* **vulnerable** to *these* **enzymes**).
2) Impaired entry; *mutation* or *deletion* of a **porins** or **proteins** *involved* in **transport** or *alteration* in **oxygen-dependent transport** *process*.
3) Impaired ribosomal binding; *mutation* or *deletion* in **receptor protein** on the **30S ribosomal** *subunit*.

- *Spectrum of activity*;
  - **Aminoglycosides** are *effective against* **majority** of **aerobic Gram -ve bacilli** *including* those that may be *multidrug resistant*, such as; *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter* **species**.
  - In *combination with* a **β-lactam** or **Glycopeptide** (**Vancomycin**): **Aminoglycosides** are *effective against staphylococci* (*including*; **MRSA**), *streptococci* and *enterococci* (*Enterococcal* **endocarditis**) (**Gentamicin** and **Streptomycin** are the *best*); **β-lactams** and **Aminoglycosides** are *administered* in 2 separate **syringe** *due to* **acid/base** *chemical interaction*.
  - **Gentamicin** and **Streptomycin** is also *useful against Francisella tularensis* (**Tularemia**; is a **pneumonia** *acquired* during **rabbit hunting** season by *hunters* **skinning** *infected* **animals**), *Yersinia pestis* (**Plague**) and *Mycobacterium* (**Tuberculosis**).
- *Updates*;
  - *Liposomal* **Gentamicin** is a *new formula* of **Gentamicin** *developed for* use in *Mycobacterium*
  - **Tobramycin** (**TOBI®**) is a *new formula* of **Tobramycin** used as *inhalation* for **Cystic Fibrosis** *developed by* Novartis and available as inhalation solution and inhalation powder (in capsules).
- *Doses*;

Agent	Usual Adult Dose	Usual Children Dose
Streptomycin	15-30 mg/kg/day OR 1-2 g IM only	20-40 mg/kg/day IM only
Gentamicin or Tobramycin	*Conventional*; 1-2.5 mg/kg/dose IV/IM every 8 or 12 hours *Once-Daily*; 4-7 mg/kg/dose IV once daily	≥ 5 years: 2-2.5 mg/kg/dose IV/IM every 8 hrs < 5 years: 2.5 mg/kg/dose IV/IM every 8 hrs
Amikacin	5-7.5 mg/kg/dose IV/IM every 8 hours (R; Lexicomp®)	
Neomycin	*Bowel Preparation*; 1 g orally every 1 hour for 4 doses followed by 1 g every 4 hours for 5 doses *Hepatic Encephalopathy* (or *Coma*); 4-12 g/day orally divided every 4-6 hours for 5-6 days	*Bowel Preparation*; 90 mg/kg/day orally divided every 4 hours for 2-3 days *Hepatic Encephalopathy* (or *Coma*); 50-100 mg/kg/day orally divided every 6-8 hours for 5-6 days
Tobramycin (TOBI®)	≥ 6 years; 300 mg every 12 hours for 28 days and followed by 28 days off drug	

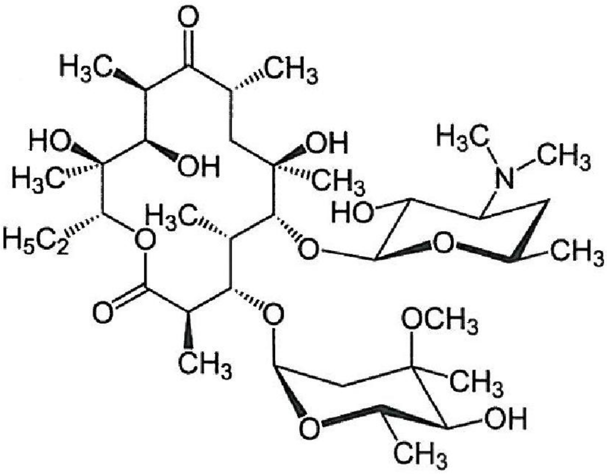
Side Effects

- Nephrotoxicity (*dose-related*);
    - **Oliguric acute nephrotoxicity** is **often** *reversible*, ***but*** it *may be* **fatal**, with a ***rise*** in the **serum creatinine**.
    - ***Retention*** of the **Aminoglycosides** by the **proximal tubular cells** cause ***leakage*** of **intracellular ions**, **proteins**, and **enzymes**. Thus, the ***resulting*** **decline** in **glomerular filtration**, the **renal function** ***returns*** **almost** to **normal**, as ***if*** the **kidney** had ***become*** **refractive**.
    - ***Risk*** of **nephrotoxicity** are ***increased by***;
        - ***Concurrent use*** of **NSAIDs**, **Diuretics**, **Cisplatin**, **Cyclosporine**, **Cephalosporins**, **Amphotericin** and **Vancomycin**.
        - **Elderly**, **renal impairment** and **pregnancy**.
    - **Once-daily dosing** ***less*** **nephrotoxic** than **divided-dose regimen** (*Not appropriate* in ***severe*** **renal impairment**, **pregnancy**, **liver failure**, and ***serious*** **illness**).
- Ototoxicity (*dose-related*);
    - **Ototoxicity** can be ***temporary*** *but* is **usually irreversible** and ***common*** **symptoms** of **inner ear damage** are: **tinnitus**, **hearing loss**, **vertigo**, **trouble** with ***coordination*** and **dizziness**.
    - **Aminoglycosides** are ***cleared more*** **slowly** *from* **inner ear fluids** than ***from*** **serum** and *therefore* a ***latency*** **exists** to the **ototoxic** ***effects*** of **Aminoglycosides**.
    - **Audiology** ***follow-up*** are ***necessary*** in **long-term** (≥ 2 weeks) **use** of **Aminoglycosides**.
- **Neuromuscular paralysis**;
    - **Aminoglycosides** ***inhibits*** **ACh** ***release*** from **cholinergic nerves** by ***competing*** with **calcium ions**.
    - This **effect** is ***particularly*** **occur**; in **high doses** or ***if*** **concurrent** ***administration*** of **neuromuscular blockers** or in ***patients*** *with* **myasthenia gravis**.
    - **Calcium gluconate** or **Neostigmine** can ***reverse*** this **effect**.
- **Allergic reactions**: **Contact dermatitis** is a ***common*** **reaction** to ***topically*** *applied* **Neomycin**.

- **Aminoglycosides** are ***pregnancy*** **category D** and ***should be*** **avoided**.

Macrolides

- **Macrolides** are a **group** of ***closely*** *related* **compounds** *characterized by* a ***large*** **macrocyclic lactone ring** (usually containing 14 or 16 atoms) to ***which*** **deoxy sugars** are ***attached***.
- ***Some*** **Macrolides** have **antibiotic** ***activity*** such as **Erythromycin**, was the ***first*** of these drugs and ***obtained*** in **1952** from ***Streptomyces erythreus***.
- **Clarithromycin** (a **methylated** ***form*** of **Erythromycin**) and **Azithromycin** (having a **larger lactone** ***ring***) are ***semisynthetic*** **derivatives** of **Erythromycin**.
- **Ketolides** are a ***class*** of **antibiotics** that are ***structurally related*** to the **Macrolides** (have ***similar*** **antimicrobial coverage**. However, the **Ketolides** are ***active against*** many **Macrolide-resistant gram +ve strains**).



Erythromycin

(The **Macrolide ring** is the lactone at upper-left)

- ***Some*** **Macrolides** have **antifungal** ***activity*** as **Polyene Antimycotics** as **Amphotericin B** & **Nystatin**.
- ***Some*** **Macrolides** have **immunomodulator** ***activity*** such as **Tacrolimus**, **Pimecrolimus** & **Sirolimus**.

Erythromycin	**Clarithromycin** (Klacid®)	**Azithromycin** (Zithromax®)
Spiramycin (Rovamycin®)	**Roxithromycin** (Roxicin®)	**Josamycin** (Josaxin®)

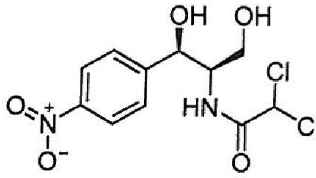
- **Erythromycin** [er-ith-roe-MYE-sin], **Clarithromycin** [klarith-roe-MYE-sin] and **Azithromycin** [a-zith-roe-MYE-sin] are the ***most common*** **Macrolides**.
- **Spiramycin** [SPIR-a-MYE-sin] has ***Antiparasitic activity*** (**Antiprotozoal**) and it is ***used*** to treat **toxoplasmosis** ***during*** **pregnancy**, but still ***not*** **approved** by **US FDA**.
- **Roxithromycin** [rok-si-throw-MYE-sin] and **Josamycin** [jo-sa-MYE-sin] are ***available*** in ***some*** **countries** (not available in the United States).

Pharmaco Kinetics

- ***Administration*** and ***Absorption***;
  - **Erythromycin base** is ***destroyed by*** **gastric acid** and ***must be*** **given** as *either* **enteric-coated** or ***more-stable*** **salts** or **esters**. **Erythromycin** ***Formulations***;
    - **Oral**;
      - **Erythromycin Base** (*and also available* **topically**).
      - **Erythromycin Ethylsuccinate** (*affected by* **food**).
      - **Erythromycin Stearate** (less *affected by* **food**).
      - **Erythromycin Estolate** (is **best-absorbed**, but it is ***contraindicated*** during **pregnancy**; ***increase*** **risk** of **hepatotoxicity**).
    - **Parenteral**;
      - **Erythromycin Gluceptate**
      - **Erythromycin Lactobionate**
  - **Clarithromycin** and **Azithromycin** are ***stable*** in **stomach acid** and are ***readily*** **absorbed**.
  - **Food** ***interferes*** with the **absorption** of **Erythromycin** and **Azithromycin** (**Azithromycin capsules** and **extended release suspension** ***should*** be ***administered*** **1 hour** ***before*** or **2 hours** ***after*** **meals**, ***while*** **Azithromycin tablets** and **immediate release suspension** can be ***taken with*** or ***without*** **food**).
  - **Food** *slightly* ***delays*** the **onset** of **Clarithromycin absorption**, but ***increases*** the ***peak*** **plasma concentration** by *about* **24%**.
  - **Erythromycin**, **Azithromycin** and **Clarithromycin** are ***available*** in **IV** ***formulations***.

Chloramphenicol

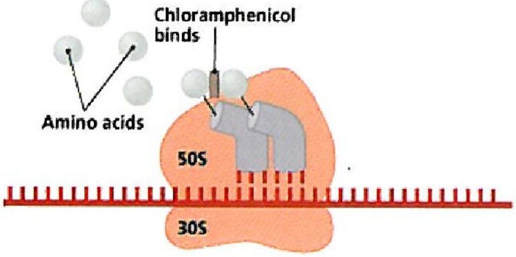
- **Chloramphenicol** was ***isolated*** from the soil organism ***Streptomyces venezuelae*** in **1947**.
- It was ***released*** in the **United States** in **1949** and was ***widely used*** in the **1950s**.
- It was the ***first* antibiotic** that was ***chemically* synthesized** in an ***efficient* process**.
- ***Because*** of **potential toxicity**, ***bacterial* resistance**; **Chloramphenicol** is ***rarely* used** in the **United States** (oral **Chloramphenicol** in the **US** ***stopped*** in **1991**).



Chloramphenicol

Chloramphenicol

- **Chloramphenicol** [klor-am-FEN-i-kole] is a ***broad-spectrum* antibiotic**.
- ***Mechanism***; **Bacteriostatic** (*may be* **Bactericidal**; ***depending on*** the **dose** and **organism**).
  - It ***binds reversibly*** to the **50S *subunit*** of the **bacterial ribosome** and ***inhibits*** **peptide bond *formation*** (***inhibit*** **peptidyl transferase**).
  - ***Due to** some* **similarity** of ***mammalian*** **mitochondrial ribosomes** to those of **bacteria**; ***high circulating*** **Chloramphenicol**, ***producing*** **bone marrow toxicity**.



- ***Spectrum***; **Chloramphenicol** is ***active against*** *many types* of **microorganisms** *including* ***Chlamydiae, Rickettsiae, Haemophilus influenzae*** and ***Neisseria meningitidis***.
- ***Resistance***; **Enzymatic inactivation**, ***impermeability*** to **Chloramphenicol** and **ribosomal *protection***.
- ***Formulations*** and ***uses***;
  - **Eye ointment** or **drops**; for **eye *infections***.
  - **Oral** (*was removed from the US market*).
  - **IV injection**; *only as* **alternative**.
    - **Typhoid fever** (***3rd generation* Cephalosporins** & **Fluoroquinolones** are ***drug of choice***).
    - **Meningitis** (***3rd generation* Cephalosporins** are ***drug of choice***).
    - **Rickettsial infection** (**Tetracyclines** are ***drug of choice***).
- ***Metabolism***; **Chloramphenicol** is ***metabolized by*** the **liver** to **Chloramphenicol glucuronate** by **glucuronidation** (*which is inactive*).
- ***Excretion***; ***Active*** **Chloramphenicol** (about 10% of the total dose administered) and its ***inactive*** **Chloramphenicol glucuronate** (about 90% of the total) are ***eliminated*** in the **urine**.

Side Effects

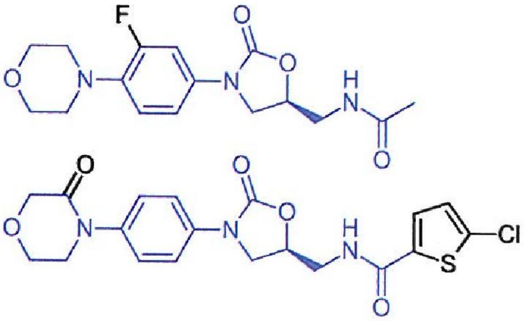
- **Anemias** (*dose-related*);
  - **Hemolytic anemia**; in **patients** *with* **glucose-6-phosphate dehydrogenase *deficiency***.
  - **Aplastic anemia** (***bone marrow suppression***); **rare**, **idiosyncratic reaction**, ***irreversible***, **independent *of* dose** and ***highest risk*** with ***oral*** **Chloramphenicol** and can be **fatal**.
  - **Other anemias**; ***reversible*** **suppression** of **red cell *production***.
- **Gray Baby Syndrome**;
  - **Neonates** have a ***low capacity*** to **glucuronidation**, and they have ***underdeveloped*** **renal function**; which ***accumulates active*** **Chloramphenicol** ***levels*** that ***interfere with*** the **function** of **mitochondrial ribosomes**.
  - This ***leads to** poor* **feeding**, ***depressed*** **breathing**, **cardiovascular collapse**, **cyanosis** (**gray baby**) and **death**.

Drug Interactions

- **Chloramphenicol** is a ***liver microsomal enzyme inhibitor***, thus ***decrease*** **metabolism** of ***other*** **drug** *such as*; **Antiepileptics** and **Anticoagulants**.
- ***Antagonizes*** the **bactericidal** ***action*** of **Penicillins** or **Aminoglycosides**.

Oxazolidinones

- **Oxazolidinones** are a *class* of **compounds** *containing* **2-oxazolidone** in the **structure**.
- **Oxazolidinones** have been ***known as*** **Monoamine Oxidase Inhibitors (MAOIs)** ***since*** the ***late*** **1950s**.
- Their **antimicrobial properties** were ***discovered*** in the **1970s**.
- *As of* **2000**, **FDA approved Linezolid** as the ***first*** **Oxazolidinone antibiotic** ***available***.
- *As of* **2014**, **FDA approved Tedizolid** as the ***second*** **Oxazolidinone antibiotic** ***available***.
- ***Other members*** of this class have entered ***development***, such as **Posizolid**, **Ranbezolid**, **Torezolid**, and **Radezolid**.
- **Rivaroxaban** (Xarelto®) is **oxazolidinone** ***derivative*** used as **anticoagulant** have ***high*** **structural similarity** with **Linezolid**.



Chemical structures of **Linezolid** (**top**) and **Rivaroxaban** (**bottom**).

Linezolid (Zyvox®) (Averozolid®)

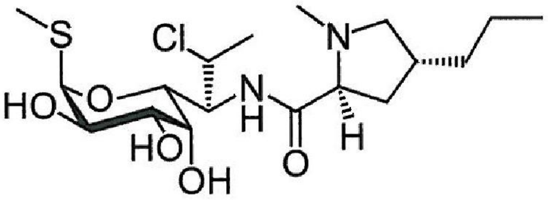
- **Linezolid** [lin-AYZ-oh-lid] is a ***synthetic*** **oxazolidinone** ***developed*** *to combat* ***resistant*** **Gram + ve** ***strains***, *such as*;- **Methicillin-resistant *Staphylococcus aureus* (MRSA)**.
    - **Vancomycin-resistant *Streptococcus aureus* (VRSA)**.
    - **Vancomycin-resistant *enterococci* (VRE)**.
    - **Penicillin-resistant *streptococci***.
- ***Advantage of*** **Linezolid** ***over*** **Tigecycline**, **Daptomycin** and **Vancomycin**;
    - **Oral** *formulation* is ***completely absorbed*** (**Bioavailability: 100%**); **IV** is also **available**.
    - ***Widely*** **distributed** ***throughout*** the **body**.
    - ***No*** **dose adjustments** are ***required*** for **renal** or **hepatic dysfunction**.
    - ***Used*** in **children** and **pregnancy** (***category* C**).
    - **Local brands** are ***less expensive***.
- ***Mechanism***; **Linezolid** ***binds*** to the **bacterial 23S ribosomal RNA** of the **50S subunit**, *thereby* ***inhibiting*** the **formation** of the **70S *initiation* complex**.
- ***Resistance***; By ***mutation of*** the **Linezolid binding site** on **23S *ribosomal* RNA**.
- ***Spectrum***; **Linezolid** is ***effective*** **against** all ***important*** **Gram + ve**;
    - ***Enterococcus faecium*** and ***Enterococcus faecalis*** (*including* **Vancomycin-*resistant enterococci***).
    - ***Staphylococcus aureus*** (*including* **Methicillin-*resistant Staphylococcus aureus***).
    - ***Streptococcus agalactiae***, ***Streptococcus pneumoniae*** and ***Streptococcus pyogenes***.
    - ***Effective against Listeria monocytogenes***, ***Corynebacterium*** **species** and ***Nocardia***.
    - **Linezolid** is also ***moderately*** **active** ***against Mycobacterium tuberculosis***.
- ***Indications***; - ***Complicated*** **Skin & Skin Structure Infections (cSSSIs)**.
    - ***Uncomplicated*** **Skin & Skin Structure Infections (uSSSIs)**.
    - **Vancomycin-*Resistant Enterococcal* (VRE) Infections**.
    - **Pneumonia**.
- ***Dose***; - ***Adult*** (≥12 years); 600 mg IV or oral *every* 12 hours; 10-14 (or 14-28 days *in VRE infections*).
    - ***Pediatric*** (<12 years); 10 mg/kg IV or oral *every* 8 hours; 10-14 (or 14-28 days *in VRE infections*).
- ***Side effects***; - ***Most common***; **GI upset**, **nausea**, **diarrhea**, **headache** and **rash**.
    - **Hematologic** (***reversible*** and *generally* **mild**); *due to* **bone marrow suppression** (*related to* **Linezolid**-*induced* ***inhibition*** of **mitochondrial protein *synthesis***);
        - ***Most common***; **Thrombocytopenia** (*mainly* occur if ***used*** *longer than* **10 days**).
        - **Anemia** and **neutropenia** *may also occur*.
    - **Others**; **Serotonin syndrome** (**Linezolid** *possesses* ***non-selective*** **monoamine oxidase inhibitor**) **optic** and **peripheral neuropathy** (**irreversible** and *mainly* occur if ***used*** *longer than* **28 days**) and **lactic acidosis** (*due to* **mitochondrial toxicity** and *mainly* occur if ***used*** *longer than* **several months**).
- ***Drug interactions***; **Monoamine Oxidase Inhibitors (MAOIs)** and ***other*** **Serotonergic Drugs**.
- ***Monitoring***; - ***Weekly*** **complete blood counts (CBC)** ***during*** **Linezolid therapy**.
    - **Treatment** last ***no more than*** **28 days**.

Tedizolid (Sivextro®)

- **Tedizolid** [ted-eye-ZOE-lid] is a ***second-generation*** **oxazolidinone** ***derivative*** that is **4-to-16-fold** ***more potent*** *against* ***staphylococci*** and ***enterococci*** compared to **Linezolid**.
- **Tedizolid** has been ***approved by*** **US FDA** in **2014**, for the ***treatment*** of **Acute Bacterial Skin** and **Skin Structure Infections** (**ABSSSI**).
- ***Differences*** *between* **Linezolid** and **Tedizolid** are ***minor*** *though*; **dose interval** & ***duration*** of **therapy**.
- ***Dose***; **≥ 18 years**; **Oral** or **IV**: **200 mg** ***once daily*** for **6 days** (Safety and efficacy have not been established in patients younger than 18 years).

Lincosamides

- The ***first*** **Lincosamide** to be ***discovered*** was **Lincomycin** in **1962**, isolated from ***Streptomyces lincolnensis*** in a **soil sample** from *County* of **Lincoln** (Lincoln is the capital of the US state of Nebraska); hence the bacterial and class name.
- The use of **Lincomycin** has been ***largely*** **superseded** by **Clindamycin** which *exhibits* ***improved*** **antibacterial activity**.
- **Clindamycin** is a ***chlorine-substituted*** *derivative of* **Lincomycin**.



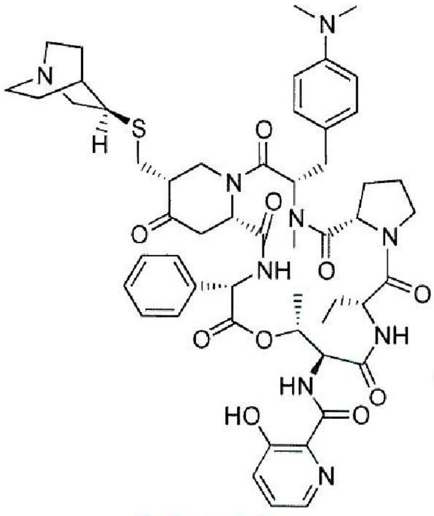
Clindamycin

Clindamycin (Dalacin®-C)

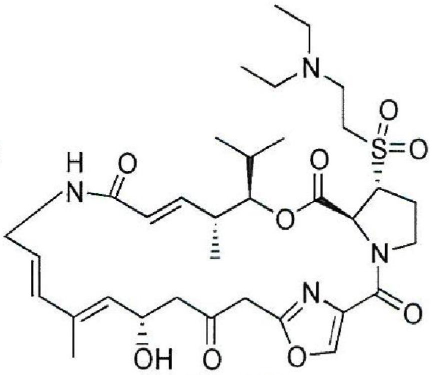
- **Clindamycin** [kiln-da-MYE-sin] ***like*** **Erythromycin**, ***inhibits*** **protein synthesis** by ***interfering*** with the **formation** of ***initiation*** **complexes** and with **aminoacyl translocation** ***reactions***.
- ***Resistance*** to **Clindamycin**, which *generally* ***confers*** **cross-resistance** to **Macrolides**.
- ***Spectrum***; **Clindamycin** is **used** ***primarily*** to treat ***many*** **Gram + ve** **anaerobes** & ***some*** of **Gram -ve anaerobes**;
  - ***Staphylococcus*** (*including* ***many*** **MRSA**) and ***Streptococcus*** (**Not** ***enterococci***).
  - ***Bacteroides***, ***Fusobacterium*** and ***Prevotella*** **species**.
  - ***Plasmodium*** **species** (**malaria**), ***Chlamydia trachomatis***, ***Pneumocystis jirovecii***, ***Toxoplasma gondii*** and ***Actinomyces*** **species**.
- ***Pharmacokinetics***;
  - ***Absorption***; **Oral** ***bioavailability***: ***rapid***; **90%**.
  - ***Distribution***; ***High*** **concentrations** in **bone**, **teeth** and **urine** ***but*** ***poor*** **entry** into the **CSF** *even* with ***inflamed*** **meninges**.
  - ***Metabolism***; **liver**.
  - ***Excretion***; **Urine** (10%) and **feces** (~4%).
  - *Accumulation* has been **reported** in **patients** *with* either ***severe*** **renal impairment** or **hepatic** *failure*.
- ***Pharmaceutical Preparations***; **Capsules**, **Ampoules**, **Solution/Lotion/Gel/Foam** 1% and **Vaginal Cream/Suppository** 2% (Oral suspension is not favored; due to its extremely foul taste and odour).
- ***Indications***; **Otitis media**, **sinusitis**, **bone** or **joint infections**, **dental infections**, **pelvic inflammatory disease**, **bacterial vaginosis**, **intra-abdominal anaerobic infections**, **pneumonia**, **endocarditis prophylaxis**, **bite wounds**, **inhalational/gastrointestinal anthrax**, **CNS toxoplasmosis**, **acne** and **malaria**.
- ***Usual Adult dose***; 150-300 mg orally *every* 6 hrs OR 600-1200 mg/day IV/IM divided *every* 12-6 hrs.
- ***Side effects***; **Diarrhea** (**pseudomembranous colitis**) **nausea** and **skin rashes**.

Streptogramins

- **Streptogramins** are a ***new class*** of **antibiotics**, *developed* ***against*** **multidrug-resistant organisms**.
- **Streptogramins A** (**Dalfopristin**) and **B** (**Quinupristin**) are ***macrolide-like*** **agents** ***naturally*** synthesized by ***Streptomyces*** **organisms**.
- They act at the **ribosomal** ***level***, ***binding*** to the **50S** ***subunit*** to ***inhibit*** **protein syntheses**.
- ***Independently***, they are **bacteriostatic**, but in ***combination*** they are ***synergistically*** **bactericidal**.



Quinupristin



Dalfopristin

Quinupristin/Dalfopristin (Synercid®)

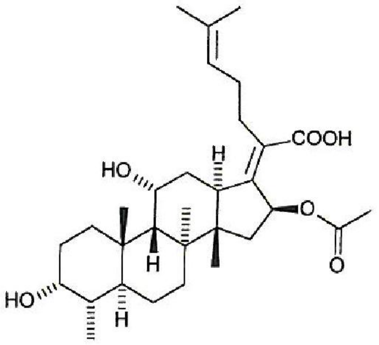
- **Quinupristin/Dalfopristin** [KWIN-ue-PRIS-tin/DAL-foe-PRIS-tin] are ***both*** **Streptogramin** ***antibiotics***, ***derived from*** **Pristinamycin** and **one** of the ***first*** **newer drugs** to ***treat*** **Vancomycin-resistant** ***enterococci*** (**VRE**) and **Methicillin-resistant** ***Staphylococcus aureus*** (**MRSA**).
- **Quinupristin** is ***derived from*** **Pristinamycin IA**; **Dalfopristin** ***from*** **Pristinamycin IIA**. They are ***combined in*** a **weight-*to*-weight** ***ratio*** of **30% Quinupristin** to **70% Dalfopristin**.
- ***Mechanism***; - The **Streptogramins** share the ***same*** **ribosomal** ***binding site*** as the **Macrolides**.
  - **Quinupristin** and **Dalfopristin** ***inhibits*** *early* and *late* phase **protein synthesis** by ***binding*** at ***different*** **sites** on the **50S bacterial ribosomal** ***subunit***.
  - The ***combination*** drug is **synergistically bactericidal** (***different*** **sites**); Synercid®
- ***Spectrum***; **Primarily** ***against*** **Gram + ve** ***cocci***, including those ***resistant*** to ***other*** **antibiotics**; ***Enterococcus faecium*** (*including* **VRE** ***strains***, **but** ***not active*** *against* ***Enterococcus faecalis***), ***penicillin-resistant*** **strains** of ***Streptococcus pneumoniae***, **Methicillin** ***susceptible*** and ***-resistant*** **strains** of ***staphylococci*** (**MSSA** and **MRSA**); **cSSSIs**, **bacteremia**, **infective endocarditis** and **intravascular catheter-associated bacteremia**.
- ***Resistance***; ***Like*** **Macrolides**; ***impaired*** **influx** or ***increased*** **efflux**, **enzymatic inactivation** and **ribosomal protection**.
- ***Dose***; IV; 7.5 mg/kg every 8-12 hours.
- ***Side effects***; - **Phlebitis** (*ideally* ***should be*** administered via a **central line**).
  - ***High incidence*** of **myalgias** (muscle pain) and **arthralgias** (Joint pain).
  - **Hyperbilirubinemia**.
- ***Drug interactions***; **Quinupristin/Dalfopristin** also ***inhibits*** **CYP3A4**.
- ***Precautions***; **Quinupristin/Dalfopristin** ***must*** be ***mixed*** and ***administered*** *with* **5% Dextrose** ***in*** **water (D5W) solutions** ***only*** (***insoluble*** and can ***crystallize*** in **normal saline**).

Pristinamycin (Pyostacine®)

- **Pristinamycin** is an ***oral*** **Streptogramins** *derived from* the ***Streptomyces pristinaespiralis***.
- **Pristinamycin** is a ***mixture*** **Pristinamycin IA 30%** and **Pristinamycin IIA 70%**.
- ***Because*** it is **usefulness** for ***severe infections*** (***lack of*** an **IV** ***formulation***) and its ***poor*** **solubility**, **Quinupristin/Dalfopristin** (**Pristinamycin-*derivatives***) was ***developed***.

Others

Fusidic Acid (Fucidin®)



- **Fusidic acid** [fue-SID-ik AS-id] is a ***steroid* antibiotic** that *derived from* the fungus ***Fusidium coccineum*** and was *developed by* **Leo Pharma** and ***released for* clinical use** in the **1960s.**
- **Fusidic acid** is ***often* used topically** but ***may*** also be given ***orally*** or ***parenterally***.
- ***Mechanism***; **Fusidic acid** is a **protein synthesis *inhibitor*** by ***preventing*** the **turnover** of **elongation factor G** (EF-G) ***from*** the **ribosome** (**bacteriostatic**).
- ***Spectrum***; **Primarily *against* Gram + ve**; *such as* ***Staphylococcus*** **species**, ***Streptococcus*** **species** and ***Corynebacterium*** **species.**
- **Fusidic acid *should not*** be used with **Quinolones**, with which they are ***antagonistic***. When ***combined*** with **Rifampicin**, the action is ***additive*** or ***synergistic***.
- ***Systemic*** **Fusidic acid *should not*** be given with **Statins** *because* of a ***risk*** of ***serious*** and ***potentially fatal* rhabdomyolysis.**

Rifaximin (Xifaxan®) (Gastrobiotic®)

- **Rifaximin** [rif-AX-i-min] is a ***new* GI antibiotic**, was ***approved by* US FDA** in **2004 *for* traveler's diarrhea, irritable bowel syndrome** and **hepatic encephalopathy**, it has ***poor* oral absorption** (**act** ***locally***).
- **Rifaximin** may use ***with*** **Vancomycin** in ***treating*** **patients *with* relapsing *Clostridium difficile***.
- ***Mechanism***; **Rifaximin *interferes*** with **transcription** by ***binding to*** the **β-subunit** of ***bacterial*** **RNA polymerase**.
- ***Dose***; - **Traveler's Diarrhea**; 200 mg orally *every* 8 hours for 3 days.
  - **Irritable Bowel Syndrome**; 550 mg orally *every* 8 hours.
  - **Hepatic Encephalopathy**; 550 mg orally *every* 12 hours.
- ***Side effects***; **Flatulence, headache, abdominal pain, bowel urgency, nausea** and **rectal tenesmus** (feeling of incomplete defecation).

Retapamulin (Altabax®) (Altargo®)

- **Retapamulin** [RE-te-PAM-ue-lin] is the ***first* drug** in the ***new class*** of **Pleuromutilin antibiotics** *developed by* **GlaxoSmithKline**, used ***topically*** for **skin infections** *such as* **impetigo.**
- **Retapamulin** was ***approved by*** the **US FDA** in **2007**.
- ***Mechanism***; **Retapamulin *inhibits* bacterial protein** *synthesis by* **interacting** at a **site** on the **50S *subunit*** of the **bacterial ribosome** (*differs from other antibiotics*).

Plazomicin

- **Plazomicin** is a ***new generation*** of **Aminoglycosides** (**Neoglycoside**).
- **Plazomicin** is being *developed by* to ***treat*** **serious infections** due to **multidrug-resistant *Enterobacteriaceae***, *including* **Carbapenem-resistant *Enterobacteriaceae*** and is in Phase III clinical trials (April 7, 2016).
- **Plazomicin** has been *reported* **synergistic *effect*** when ***combined with*** **Daptomycin** or **Ceftobiprole *against* MRSA** and **VRSA** and ***against Pseudomonas aeruginosa*** when ***combined with*** Cefepime, **Doripenem**, **Imipenem** or **Piperacillin/Tazobactam.**

Mupirocin (Bactroban®)

- **Mupirocin** [mue-PIR-oh-sin] (**Pseudomonic acid**) is a ***natural substance*** produced by ***Pseudomonas fluorescens***.
- It is ***rapidly*** **inactivated *after* absorption**, and **systemic *levels*** are ***undetectable***, so it is **used *only*** as **topical preparations (3 times daily).**
- **Mupirocin** is a **protein synthesis inhibitor** that is ***useful*** in treating **impetigo** and *other* **Gram + ve cocci *including* MRSA.**
- **Mupirocin *should not*** be *applied for* ***longer than*** **10 days** to ***avoid*** **bacterial resistance.**

Nucleic Acid Inhibitors

Quinolones and Fluoroquinolones

Antifolates

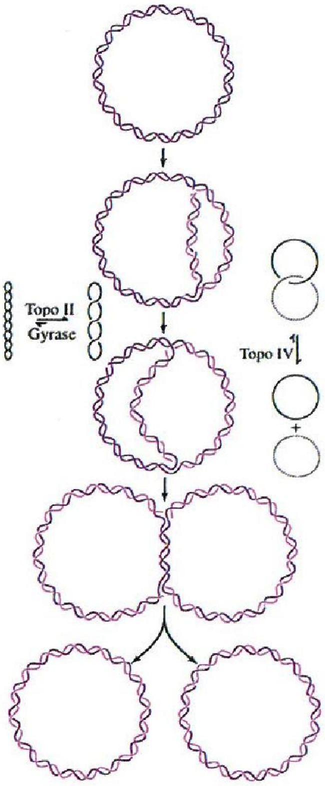
Classification According to Generation

First	**Second**	**Third**	**Fourth**
Quinolones	Fluoroquinolones		
Nalidixic acid **Cinoxacin**	**Ciprofloxacin** **Norfloxacin** **Ofloxacin** **Enoxacin** **Pefloxacin** **Lomefloxacin**	**Levofloxacin** **Sparfloxacin** **Grepafloxacin**	**Trovafloxacin** **Moxifloxacin** **Gatifloxacin** **Gemifloxacin**
- First generation ⇨ Quinolones. - Second, Third and Fourth ⇨ Fluoroquinolones. - First generation less used today. - Moderate activity against Gram - ve. - Nalidixic acid is the first quinolone drug (was introduced in 1962) during the manufacture of Quinine.	- Expanded activity against Gram - ve (including *Pseudomonas* species) - Some activity against Gram + ve. - Some activity against atypical bacteria such as Mycoplasma and Chlamydia.	- Retain expanded Gram - ve activity - Improve activity against gram +ve and atypical bacteria.	- They are also called respiratory Fluoroquinolones. - Improve activity against Gram +ve. - Gains anaerobic coverage.

There is another classification (1997) includes only Trovafloxacin in fourth generation

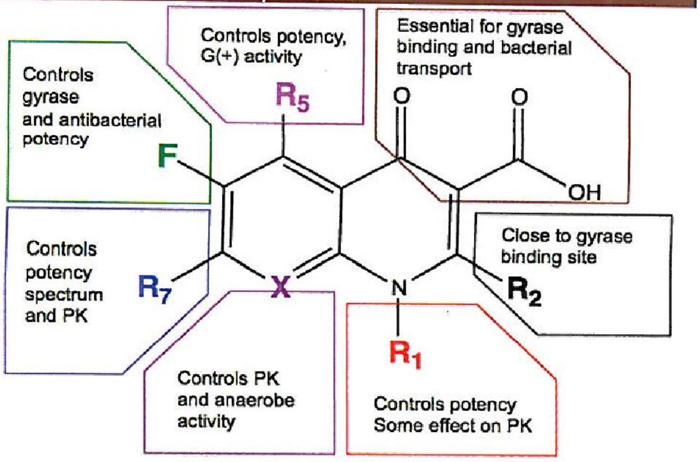
➢ Bacterial Nucleic Acid Synthesis:-

- **Bacterial chromosomes** are *double-stranded* **DNA** and *almost always* **circular.**
- **DNA** is a *stable* **molecule** *composed of* **two** *linear* **chains.**
- **DNA replication** *requires* the **uncoiling** and **separation** of the **two** *strands*.
- **DNA replication** *employs* a *large number* of **proteins** and **enzymes,** each of which **plays** a **critical role** *during* the **process;**
- **Helicase**; *Unwinds* and *separates* the **two strands** of the **DNA double helix.**
- **DNA polymerases**; *Copy* **DNA sequences** by *using* **one strand** as a *template*.
- **Topoisomerases**; *Regulates* **DNA supercoiling.**
  - *****DNA gyrase** or **Topoisomerase II**; *Relaxation* **DNA supercoiling.**
  - *****Topoisomerase IV**; *Separation* of *newly* **replicated DNA.**
- **Fluoroquinolones** *enter* **bacteria** through **porin channels** and *exhibit* **antimicrobial effects** on **DNA gyrase** (**Topoisomerase II**) and **Topoisomerase IV.**
- **Topoisomerases** are *present* in *both* **prokaryotic** and **eukaryotic cells,** *but* **Fluoroquinolones** are *specific* **inhibitors** of ***bacterial*** **Topoisomerases.**
- ***Eukaryotic*** **Topoisomerase** ***Inhibitors***, such as **Irinotecan** and **Etoposide**, are used as **antineoplastic drugs** to *kill* **cancer cells.**
- **Rifampicin** *inhibits* **bacterial RNA** *polymerase*.



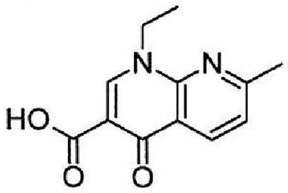
- ***Over* 10,000 Fluoroquinolone analogs** have been **synthesized**, including ***several*** with *wide* **clinical applications**
- **Fluoroquinolones** available for ***systemic* use** in the **US** include; **Ciprofloxacin**, **Levofloxacin**, **Ofloxacin**, **Gemifloxacin** and **Moxifloxacin**.

Structure-Activity Relationship

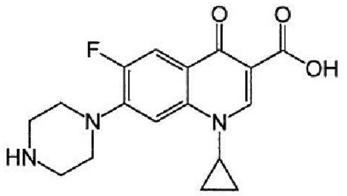

Controls potency, G(+) activity
Essential for gyrase binding and bacterial transport
Controls gyrase and antibacterial potency
R5
O
O
F
OH
Close to gyrase binding site
Controls potency spectrum and PK
R7
X
N
R2
R1
Controls PK and anaerobe activity
Controls potency Some effect on PK

PK; Pharmacokinetics

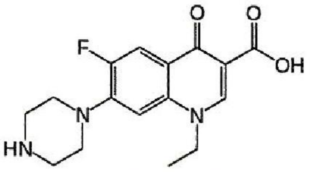
- **X**; **Carbon atom** in **Cinoxacin**, **Norfloxacin**, **Ofloxacin**, **Ciprofloxacin**, **Sparfloxacin**, **Grepafloxacin**, **Levofloxacin**, **Moxifloxacin** and **Gatifloxacin**.
- **X**; **Nitrogen atom** (**Naphthyridone**) in **Nalidixic acid**, **Enoxacin**, **Trovafloxacin** & **Gemifloxacin**.
- ***Position 1***;
  - **Cyclopropyl group** in **Ciprofloxacin**, **Sparfloxacin**, **Gatifloxacin**, **Gemifloxacin** and **Moxifloxacin** also ***increases*** the **potency** of *this* **drugs**.
  - **2,4 Di-fluoro-phenyl group** in **Trovafloxacin** also ***improves*** **potency**, ***especially*** in ***improving*** **activity *against* anaerobes**.
- **Position 5**;
  - NH_2 **group** in **Sparfloxacin *resulted*** in a *general* ***increase*** in **Gram +ve bacteria**.
  - ***Substitution*** at this **position** may have a *role* in ***severe* QT prolongation** and ***sudden* death** (**Grepafloxacin** & **Sparfloxacin** was ***withdrawn from most* countries**).
- **Position 7**;
  - **Pyrrolidine ring** (*five-membered*) in **Gemifloxacin**; is associated with ***enhanced* potency *against* Gram +ve bacteria**. *However*, this group is ***associated*** *with* ***low* water solubility** and ***low* oral bioavailability**.
  - **Piperazine ring** in **Ciprofloxacin**, **Norfloxacin** and **Enoxacin**, ***confer*** **potency *against* Gram -ve bacteria** and ***expense*** of **activity *against* *Pseudomonas aeruginosa*** (**Piperazine ring** may ***play*** a **role** in ***inhibiting*** **efflux mechanisms**). **Piperazine** is ***alkylated*** in **Levofloxacin**, **Gatifloxacin**, **Sparfloxacin** and **Ofloxacin**.
  - **Azabicyclo group** in **Moxifloxacin** and **Trovafloxacin** with ***significant*** **activity *against* Gram +ve bacteria**, ***marked*** **lipophilicity** & ***long*** **half-life**
- **Position 8** (***Photo-reactivity***);
  - **Fluorine** in **Sparfloxacin *producing most*** **phototoxic *potential***.
  - **Methoxy group** in **Moxifloxacin** and **Gatifloxacin *producing least*** **phototoxic**.



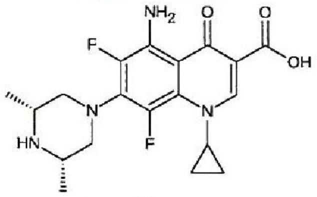
Nalidixic acid



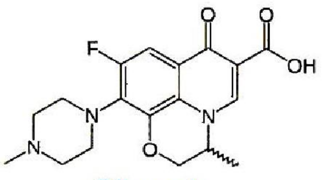
Ciprofloxacin



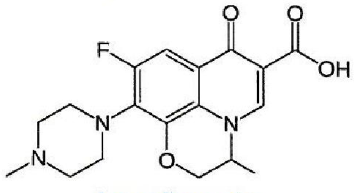
Norfloxacin


NH2
O
O
F
OH
N
N
HN
F

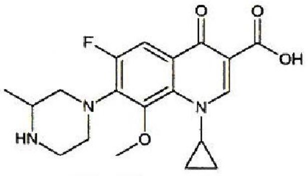
Sparfloxacin



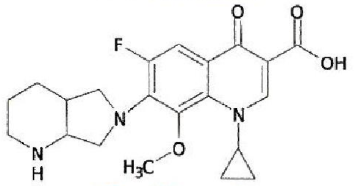
Ofloxacin



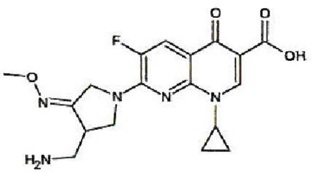
Levofloxacin


O
O
F
OH
N
N
HN
O

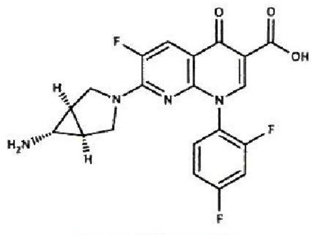
Gatifloxacin


O
O
F
OH
N
N
N
H
H3C
O

Moxifloxacin


O
O
F
OH
O
N
N
N
N
H2N

Gemifloxacin


O
O
F
OH
H
N
N
N
H2N
H
F
F

Trovafloxacin

First Generation

Nalidixic acid (NegGram®)

- **Nalidixic acid** [nal-i-DIX-ik AS-id] is the ***first*** of the ***synthetic*** **quinolone antibiotics**, used for **urinary tract infections**, it is ***effective*** **primarily** ***against*** **gram -ve bacteria**.
- **Nalidixic acid** is ***no longer*** **clinically used**.

Second Generation

Ciprofloxacin (Cipro®)	**Norfloxacin** (Noroxin®)	**Ofloxacin** (Tarivid®)
Enoxacin (Penetrex®)	**Pefloxacin** (Peflox®)	**Lomefloxacin** (Maxaquin®)

- **Ciprofloxacin** [SIP-roe-FLOX-a-sin], **Norfloxacin** [nor-FLOX-a-sin], **Ofloxacin** [oh-FLOX-a-sin] are the ***most common*** **second generation Fluoroquinolones**.
- **Enoxacin** [ee-NOX-ah-sin] **Pefloxacin** [pe-FLOX-a-sin] and **Lomefloxacin** [low-meh-FLOX-ah-sin] may also ***available*** in **some countries**.

Third Generation

Levofloxacin (Tavanic®)	**Sparfloxacin** (Parox®)	**Grepafloxacin** (Raxar®)

- **Levofloxacin** [LEE-voe-FLOX-a-sin] is **L-*isomer*** of **Ofloxacin** and the ***most common*** **used** and ***only*** **third generation Fluoroquinolones** ***available*** in **US** and ***most*** of **countries**.
- **Sparfloxacin** [spar-FLOX-a-sin] is ***also available*** in ***some*** **countries** ***like*** **Egypt**.
- **Grepafloxacin** [grep-a-FLOX-a-sin] was ***withdrawn*** **worldwide** in **1999**, ***leading to*** **QT interval** ***prolongation***, **cardiac** ***events*** and **sudden death**.

Fourth Generation

Trovafloxacin (Trovan®)	**Moxifloxacin** (Avalox®)
Gemifloxacin (Factive®)	**Gatifloxacin** (Tequin®)

- **Trovafloxacin** [troe-va-FLOCKS-ah-sin] was ***withdrawn*** from the **market** due to the ***risk*** of ***fatal*** **hepatotoxicity**.
- **Moxifloxacin** [MOX-i-FLOX-a-sin], **Gemifloxacin** [JEM-i-FLOX-a-sin] and **Gatifloxacin** [ga-ti-FLOKS-a-sin] are ***fourth*** **generation Fluoroquinolones** with ***improved*** **activity against Gram +ve organisms**, *particularly* ***Streptococcus pneumoniae*** and *some* ***Staphylococci***.

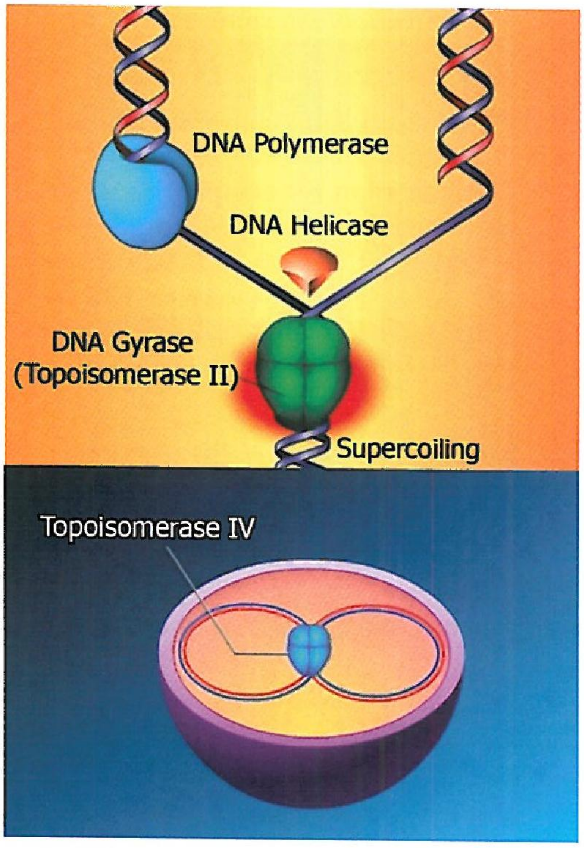
Pharmaco Kinetics

- ***Absorption***;
  - *All* **Fluoroquinolones** are ***rapidly*** **absorbed**; **bioavailability**; **80-95%**, **Norfloxacin**, **Gemifloxacin** and **Ciprofloxacin** are *lower* **bioavailability**.
  - **Calcium**, **Iron**, **Zinc**, **Sucralfate** and **Antacids** ***reduce*** the **absorption**; ***oral*** **Fluoroquinolones** ***should be*** **taken 2 hours** ***before*** or **4 hours** ***after*** *any* **products** ***containing these*** **cations**.
  - ***Ophthalmic preparations*** of **Ciprofloxacin** (Ciloxan®), **Levofloxacin** (Quixin®), **Gatifloxacin** (Zymar®) and **Moxifloxacin** (Vigamox®) and **IV** ***preparations*** of ***this drugs*** are ***available***.
- ***Distribution***;
  - *All* **Fluoroquinolones** are ***distributed*** **widely** in **body fluids** and **tissues**.
  - **Concentrations** are ***above*** *those* in **serum** in **bone**, **urine**, **kidney**, **prostatic** and **lungs**;
    - ***Lowest*** **urine concentrations** are **Moxifloxacin** and **Gemifloxacin** (***not used*** in **UTIs**).
    - ***Highest*** **urine concentrations** are **Gatifloxacin** and **Levofloxacin** (*excreted* by the **kidney** completely **unchanged**).
  - **Ciprofloxacin** and **Ofloxacin** have ***good penetration*** into **cerebrospinal fluid** in ***patients with*** **inflamed meninges**.

Pharmaco Kinetics

- ***Metabolism***;
  - *Hepatic* **metabolism** is **essential** for *clearance* of **several Fluoroquinolones.**
- ***Excretion***;
  - *Most* **Fluoroquinolones** are *excreted* **renally** (**dosage adjustments** are *needed* in **renal dysfunction**).
  - **Moxifloxacin** is *excreted* **primarily** by the **liver** (*no dose* **adjustment** is *required for* **renal impairment, while dosage adjustments** are *needed* in **liver dysfunction**).
  - **Levofloxacin**, **Gemifloxacin**, **Gatifloxacin** and **Moxifloxacin** has *relatively* **long half-lives**, *permit once-***daily dosing.**

- ***Mechanism***; **Bactericidal**;
  - **Fluoroquinolones** *block* **bacterial DNA** *synthesis* by *inhibiting* **bacterial Topoisomerase II** (**DNA Gyrase**) and **Topoisomerase IV**.
  - *Inhibition* of **DNA Gyrase** *prevents* the **relaxation** of *positively* **supercoiled DNA** that is *required* for *normal* **transcription** and **replication**, *promoting* **DNA strand** *breakage* (*more significant* in **Gram -ve**).
  - *Inhibition* of **Topoisomerase IV** *interferes* with **separation** of *newly* **replicated DNA** (*more significant* in **Gram +ve**).
  - **Agents** with *higher* **affinity** for **Topoisomerase II** (*such as* **Ciprofloxacin*** and **Levofloxacin**) *more potent* **activity** *against* ***Pseudomonas aeruginosa*** and *should not* be **used** for ***Streptococcus pneumoniae*** **infections**.
  - **Agents** with *higher* **affinity** for **Topoisomerase IV** (*such as* **Moxifloxacin***, **Gemifloxacin** and **Gatifloxacin**) *more potent* **activity** against ***Streptococcus pneumoniae*** and *should not* be used for ***Pseudomonas aeruginosa*** **infections**.



Bacterial Resistance

1) ***Impaired* influx** or ***increased* efflux**.
2) **Chromosomal mutations**; *both* **Topoisomerase II** and **Topoisomerase IV** may *undergo* **mutations** (*alteration* of the **target sites**);
   - ***Mutation*** in **Topoisomerase IV** will ***occur* first** in **Gram +ve *organisms***.
   - ***Mutation*** in **Topoisomerase II** and ***active* efflux** will ***occur* first** in **Gram -ve *organisms***.

- ***Spectrum of activity***;
  - **Quinolones** such as **Nalidixic acid** did *not achieve* **systemic antibacterial** *levels* and were **useful** *only* in the **treatment** of *lower* **Urinary Tract Infections** (**UTIs**).
  - **Fluorinated** *derivatives* (**Fluoroquinolones**) *achieve* **bactericidal** *levels* in **blood** and **tissues**.
  - **Fluoroquinolones** were *originally* **developed** *because* their *excellent* **activity** *against* **Gram -ve aerobic** *bacteria*; *Escherichia coli*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Proteus mirabilis*, *Shigella* **species** and *Enterobacter* **species**.
  - *Several* **newer agents** have *improved* **activity** *against* **Gram +ve** *cocci*.

- **Norfloxacin** is the ***least* active** of the **Fluoroquinolones** ***against** both* **Gram -ve** and **Gram +ve organisms** and ***infrequently* prescribed** *due to* ***poor*** **oral bioavailability** & a ***short*** **half-life.**
- **Ciprofloxacin**, **Enoxacin**, **Lomefloxacin**, **Ofloxacin**, **Levofloxacin** and **Pefloxacin** ***possessing excellent*** **Gram -ve *activity*** and ***moderate*** to ***good*** **activity *against* Gram +ve *bacteria*.**
- **Ciprofloxacin** (**THE BEST**) and **Levofloxacin** are the ***most potent*** **activity *against Pseudomonas aeruginosa.***
- **Levofloxacin** has ***superior*** **activity *against*** **Gram +ve *organisms***, including ***Streptococcus pneumoniae.***
- **Moxifloxacin** (**THE BEST**), **Gatifloxacin** & **Gemifloxacin** ***improved*** **activity *against*** **Gram +ve *organisms, particularly Streptococcus pneumoniae*** and ***some staphylococci.***
- **Moxifloxacin** is the ***only approved*** has ***modest*** **activity *against*** **anaerobic *bacteria*.**

Indications

- **Ciprofloxacin;**
  * **Urinary Tract Infections;** *Adult and Children*
  * ***Chronic* Bacterial Prostatitis.**
  * **Urethral & Cervical Gonococcal Infections.**
  * **Infectious Diarrhea.**
  * **Typhoid Fever.**
  * **Anthrax** (*prophylaxis* and *treatment*); *Adult and Children*
  * **Plague** (*prophylaxis* and *treatment*); *Adult and Children*
  - **Empirical Therapy** in **Febrile Neutropenic Patients.**
  - **Intra-abdominal Infections.**
  - **Bone & Joint Infections.**
  - **Skin/Skin Structure Infections.**
  - ***Acute* Sinusitis.**
  - ***Nosocomial* Pneumonia.**
  - ***Lower* Respiratory Tract Infections.**
  - ***Non-cystic* Fibrosis Bronchiectasis;** *Dry powder for inhalation.*
- **Levofloxacin;**
  * ***Uncomplicated* Urinary Tract Infections.**
  * ***Complicated* Urinary Tract Infections & Acute Pyelonephritis.**
  * ***Chronic* Bacterial Prostatitis.**
  * **Anthrax** (*prophylaxis* and *treatment*); *Adult and Children*
  * **Plague** (*prophylaxis* and *treatment*); *Adult and Children*
  - ***Acute* Bacterial Sinusitis;** *Adult (and Children off-label)*
  - ***Community*-Acquired Pneumonia;** *Adult (and Children off-label)*
  - ***Acute* Bacterial Exacerbation** of **Chronic Bronchitis.**
  - ***Nosocomial* Pneumonia.**
  - ***Pseudomonas aeruginosa*** **Pulmonary Infections** (Quinsair®); Inhalation.
  - **Skin/Skin Structure Infections.**
  - **Epididymitis** and **Acne Vulgaris** (*Off-label*).
- **Moxifloxacin;**
  * ***Acute* Bacterial Sinusitis.**
  * ***Community*-Acquired Pneumonia.**
  * ***Acute* Exacerbation** of **Chronic Bronchitis.**
  * **Skin & Skin Structure Infections.**
  - **Intra-abdominal Infections.**
  - **Pneumonic & Septicemic Plague.**
- **Fluoroquinolones** has also ***activity against M. tuberculosis.***
- **Ofloxacin** and **Levofloxacin** are ***second line therapy*** for ***Chlamydia*** **Infection** *after* **Azithromycin 1 g** ***single dose*** or **Doxycycline 100 mg** ***twice*** daily *for* **7 days.**

- ***Doses***; **Ciprofloxacin** and **Levofloxacin** are ***available as* oral suspensions** in ***many* countries.**

Agent	Usual Adult Dose	Usual Children Dose
Ciprofloxacin	500-750 mg orally every 12 hours OR 400 mg IV every 12 hours	10 mg/kg orally or IV every 12 hours (**Ciprofloxacin** and **Levofloxacin** are the *only* **Fluoroquinolones *used*** in **pediatrics** and **children**); *see indications*
Norfloxacin	400-800 mg orally every 12 hours	<18 years: Safety and efficacy not established
Ofloxacin	200-400 mg orally every 12 hours	<18 years: Safety and efficacy not established
Levofloxacin	500-750 mg orally/IV every 24 hours	8 mg/kg orally/IV every 12 hours
Moxifloxacin	400 mg orally/IV every 24 hours	<18 years: Safety and efficacy not established
Gatifloxacin	200-400 mg orally/IV every 24 hours	<18 years: Safety and efficacy not established
Gemifloxacin	320 mg orally every 24 hours	<18 years: Safety and efficacy not established

Side Effects

- **In general**; **Fluoroquinolones** are ***generally* well tolerated. Like *most* antibiotics**, the ***most common* side effects** are **nausea**, **vomiting** and **diarrhea**.
- **Nervous system**;
  - **CNS**; - ***Common***; **Headache**, **dizziness** and **insomnia**.
    - ***Less common***; **Hallucinations** and **depression**.
    - ***Rare***; **Neurotoxicity** (**Seizures**) ***inhibit* GABA**; [*especially with* **Norfloxacin** and **Ciprofloxacin**]; ***Only* in patients *underlying* neurologic diseases (epilepsy), *renal* insufficiency** or ***concomitant* use of neurotoxic drug.**
  - **PNS**; **Peripheral neuropathy** *can also occur*.
- **Cardiovascular**;
  - **QT interval *prolongation*** [*especially with* **Levofloxacin**, **Gatifloxacin**, **Gemifloxacin** and **Moxifloxacin**].
  - **Moxifloxacin** ***carries*** the ***greatest*** **risk**, *while* **Ciprofloxacin** ***appears to*** be ***associated with*** the ***lowest*** **risk.**
- **Dermatologic**;
  - **Photosensitivity**; ***Severe* sunburns *may occur***; can be ***avoided*** or ***prevented* by *avoiding*** *exposure* to **sunlight** or ***should be*** *advised to* ***use*** **sunscreen *while* taking Fluoroquinolones.**
- **Musculoskeletal**;
  - **Articular Cartilage Erosion** (**Arthropathy**) has ***been observed. Thus*, these drugs** are ***not routinely*** *recommended for* **patients *under* 18 years *of* age** (***Except***; **Ciprofloxacin** and **Levofloxacin** in ***some* indications**).
  - **Tendon rupture**; a ***rare* complication** that has been ***reported in* elderly**, ***patients with* renal dysfunction** and ***those* taking Corticosteroids.**
- **Glucose Metabolism**;
  - **Gatifloxacin** has been ***associated with* hyperglycemia** in **diabetic patients** and *with* **hypoglycemia** in **patients** also ***receiving* oral hypoglycemic *agents*** (*was withdrawn in US in* 2006).
- **In 2016**; **FDA** *required* the ***addition*** of a **warning** for all systemic **Fluoroquinolones** that *their* **risks *outweigh*** *their* **benefits** for ***most cases*** of **sinusitis**, **bronchitis**, and ***uncomplicated* UTIs *unless* other options** are ***not* available.**

* ***Pregnancy***; **Fluoroquinolones *should be* avoided** *during* **pregnancy** in the ***absence of* specific data *documenting* their safety (Category C).**

Drug Interactions

- **Fluoroquinolones** *form* **chelates** with **divalent cations**; *particularly* **Aluminum** and **Magnesium** and, to a ***lesser degree***, **Iron**, **Zinc** and **Calcium**.
- **Quinolones** may also ***raise*** the **serum levels** of **Warfarin**, **Caffeine** and **Cyclosporine**.
- **Fluoroquinolones** with ***topical*** **Tretinoin** ***increase risk*** of **phototoxicity**.
- **Ciprofloxacin** can ***increase*** **serum levels** of **Theophylline** by ***inhibiting*** its **metabolism**.
- A ***potentially dangerous interaction*** was ***recently found*** between **Ciprofloxacin** and **Tizanidine** (Sirdalud®); The ***interaction*** resulted in a ***severe*** **decrease** in **blood pressure** and ***enhanced*** **CNS effects** of **Tizanidine**.

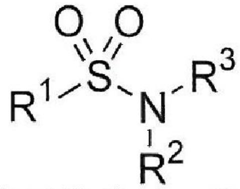
Patient Counselling

*** Fluoroquinolones Precautions ***

1) ***Don't take*** with **calcium-rich foods** as; **milk & milk products**.
2) ***Don't take*** with ***other drugs*** *specially*; **Ca**, **Iron** and **Antacids**.
3) ***Don't take*** with **Corticosteroids** ***especially*** in **elderly** and **patients** ***with*** **renal dysfunction**.
4) ***Don't used*** for **children** ***less than*** **18 years** and **pregnancy**.
5) ***Used cautiously*** in **epileptic patients**.
6) ***Avoid*** **sun exposure** **OR** ***Use*** **sun screen**.
7) ***Need*** **dose adjustment** in **kidney failure** (*except* **Moxifloxacin**).

Antifolate Antibiotics

- **In 1932**; **German scientists Josef Klarer**, **Fritz Mietzsch**, and **Gerhard Domagk** *discovered* the **antibacterial activity** of a **synthetic dye** (**Prontosil®**) that could treat *streptococcal* and *staphylococcal* infections in mice, at the **Bayer** *Laboratories*. **Prontosil®** is ***first*** **sulfonamide drug**.
- **Sulfonamides** (*also called* **sulphonamides**, **sulfa drugs** or **sulpha drugs**) are a ***family*** of **antibiotics** that ***inhibit*** **synthesis** of **folate**. *Therefore*, in the ***absence*** of **folate**, cells ***cannot*** **grow** or **divide**.
- **Humans** ***obtain*** **folates** ***from*** the **diet**. *In contrast*, ***many*** **bacteria** are ***impermeable*** to **folates** and, therefore, ***must synthesize*** **folate**.
- **Dihydrofolate Reductase** (**DHFR**) ***inhibitor*** (**Trimethoprim** and **Pyrimethamine**) ***inhibits conversion*** of **Dihydrofolic acid** ***to*** **Tetrahydrofolic acid** (*active form*).



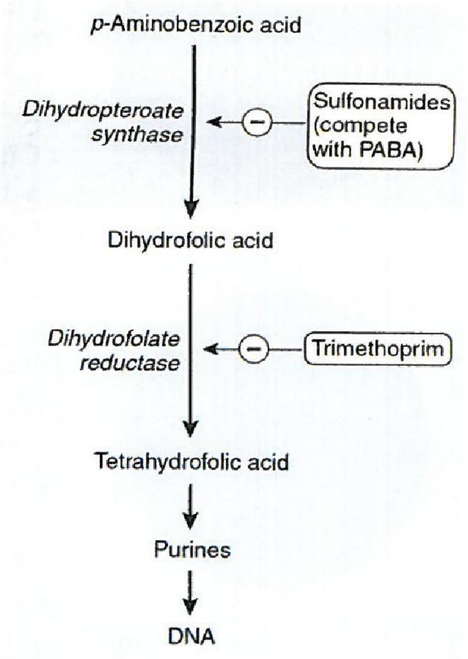
Sulfonamide Functional Group

- ***Some*** **sulfonamides** ***without*** **antibacterial activity**; *such as* **sulfonylureas** (**antidiabetic**), **thiazide diuretics** and **Celecoxib** (**COX-2 inhibitors**).
- **Allergies** to **sulfonamides** are ***common***.
- **Sulfonamides** have the ***potential*** to **cause** a *variety of* **untoward reactions**.
- **Sulfonamides** are ***seldom*** **prescribed** ***alone*** *except* in **developing countries**, where they are ***still employed*** because of their ***low*** **cost** and **efficacy**.
- ***Common*** **Sulfonamides** (*Examples*);
  - ***Systemic***; - ***Well absorbed***; - ***Short***; **Sulfanilamide** (Prontosil®), **Sulfacytine**, **Sulfisoxazole** (**Sulfafurazole**), **Sulfamethizole**, **Sulfadimidine** and **Sulfaisodimidine**.
    - ***Intermediate***; **Sulfamethoxazole**, **Sulfadiazine** and **Sulfapyridine**.
    - ***Long***; **Sulfadoxine**, **Sulfamerazine** and **Sulfamethoxydiazine**.
    - ***Poorly absorbed***; **Sulfasalazine** (for **Inflammatory Bowel Disease**), **Sulfaguanidine** & **Sulfathalidine**.
  - ***Topical***; - ***Ophthalmic***; **Sulfacetamide** (Isopto Cetamide®).
    - ***Skin***; **Silver Sulfadiazine** (Dermazine®) for **skin burns** and **Mafenide** (Sulfamylon®).
- ***Combining*** the **Sulfonamide** (**Sulfamethoxazole**; **SMX**) with **DHFR** ***inhibitor*** (**Trimethoprim**; **TMP**); the **generic name** for the ***combination*** is **Cotrimoxazole**; ***provides*** a **synergistic combination**.

Co-Trimoxazole (Sulfamethoxazole/Trimethoprim) (Septrin®)

- **Cotrimoxazole** OR **Sulfamethoxazole (SMX)/Trimethoprim (TMP)** [sul-fa-meth-OKS-a-zole / trye-METH-oh-prim] is the ***most widely*** used **antifolate antibiotic**.
- **Cotrimoxazole** is a ***broad-spectrum*** **antibacterial agent** ***inhibit*** *both* **Gram +ve** and **Gram -ve** ***bacteria*** and ***some*** **protozoa**.
- ***Mechanism of action***; **Cotrimoxazole** ***blocks*** **2 consecutive** ***steps*** in the ***biosynthesis*** of **nucleic acids** in ***many*** **bacteria**.
  1) ***Due to*** **structural similarity** *between* **Sulfonamides** & **P-Amino-benzoic acid (PABA)** ⇨ ***Compete*** with **PABA** ⇨ ***Inhibition of*** **Dihydropteroate synthase**.
  2) **Trimethoprim** ***inhibits*** **Dihydrofolate reductase**.

  * From **1** and **2** ⇨ ***Inhibit*** *of* **Folic acid** ***synthesis*** which is ***essential for*** *synthesis of* **DNA**.



- ***Advantage of combination*** (SMX/TMP);
  - **Synergistic effect.**
  - ***Decrease*** the **dose** of **each one**.
  - ***Decrease*** the **bacterial resistance**.
  - ***Increase*** the **spectrum of activity**.
  - **Bactericidal action.**
- ***Spectrum of activity***; ***Staphylococcus aureus*** (*including* many **MRSA strains**), ***Streptococcus pneumoniae***, ***Streptococcus pyogenes Haemophilus influenzae***, ***Escherichia coli***, ***Salmonella***, ***Shigella***, ***Klebsiella pneumoniae***, ***Nocardia***, ***Stenotrophomonas maltophilia***, ***Listeria monocytogenes*** & ***Pneumocystis jirovecii***.
- ***Resistance***; may occur as a result of mutations that cause;
  1) ***Overproduction*** of **PABA**.
  2) ***Production*** of a **folic acid-synthesizing enzyme** that has ***low*** **affinity** for **Sulfonamides**.
  3) ***Impair*** **permeability** to the **Sulfonamide**.
- ***Indications***; **Urinary tract infections**, **respiratory tract infections** and **gastrointestinal tract infections** and ***other*** **infections** caused by ***sensitive*** **organisms**.
- ***Dose***; **TMP/SMX** *comes* in a ***fixed*** **1:5 ratio** of the ***two*** **components**.
  - **Oral tablets**; - ***Single-strength***; Septrin® (80:400 mg **TMP:SMX**).
    - ***Double-strength***; Septrin-D.S.® (160:800 mg **TMP:SMX**); 1-2 tab. orally every 12-24hr.
  - **Oral Suspension**; **>2 months**; 8-10 mg **TMP**/kg/day PO divided every 12hr.
  - **IV**; 8-20 mg **TMP**/kg/day IV *every* 6-12hr.
- ***Side Effects***; - **Dermatologic**: - **Rash** (***much*** **more common** in **AIDS patients** and ***severe*** in **elderly**).
    - **Stevens-Johnson syndrome** *also occur but* **rare**.
  - **GIT**; **Nausea**, **vomiting** and **diarrhea**.
  - **Hematologic**; - **Bone-marrow suppression** (dose-dependent).
    - **Hemolytic anemia**; *may occur* in **patients** *with* **G6PD** ***deficiency***.
  - **Renal**; **Crystalluria** (blood urea and creatinine elevations), **acute interstitial nephritis** and can ***lead to*** **acute renal failure** (*very rare*).
  - **Electrolytes**; **Hyperkalemia**.
  - **Newborns**; **Kernicterus** (Bilirubin-induced brain dysfunction; Neurotoxic hyperbilirubinemia).
- ***Contraindications***; **hypersensitivity** to **sulfa**, **Age <2 months**, **CrCl <15 mL/min**, **G6PD deficiency (Favism)**, **hepatic impairment**, **pregnancy** and **nursing mothers**.
- ***Drug interactions***; - ***Increase*** **concentration** of **Phenytoin** and **Warfarin** (inhibit metabolism).
  - ***Increase*** **concentration** of **Methotrexate** (displacement from plasma proteins).
- **N.B.**; - **Trimethoprim** is ***about*** **50,000 times** ***less efficient*** in ***inhibition*** of **mammalian Dihydrofolic acid reductase**.
  - **Trimethoprim** is **20- to 50-fold** ***more*** **potent** ***than*** the **Sulfonamides**.

Sulfadiazine/Pyrimethamine

- **Sulfadiazine/Pyrimethamine** [sul-fa-DYE-a-zeen/peer-i-METH-a-meen] is used ***for*** **Toxoplasmosis**.

Sulfadoxine/Pyrimethamine (Fansidar®)

- **Sulfadoxine/Pyrimethamine** [sul-fa-DOX-een/peer-i-METH-a-meen] is used as **antimalarial drug**.

Urinary Tract Antiseptics

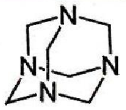
- **Urinary tract infections (UTIs)** are ***prevalent*** in **women** *of* **child-bearing age** and in the **elderly** *population*.
- ***Escherichia coli*** is the ***most common*** **pathogen**, causing *about* **80%** of ***uncomplicated upper*** and ***lower*** **UTIs**.
- ***Staphylococcus saprophyticus*** is the ***second*** **most common bacterial pathogen** causing **UTIs**.
- *In addition to* **Fluoroquinolones**, **Cotrimoxazole** and **Fosfomycin UTIs** may be ***treated with*** any **one** of a **group** of **agents *called* urinary tract antiseptics**.
- **Urinary tract antiseptics *do not* achieve antibacterial levels** in the **circulation**, but because they are ***concentrated*** in the **urine**, **microorganisms** at that **site** can be ***effectively*** **eradicated**.

Nitrofurantoin (Uvamin® retard) (Macrodantin®) (Macrobid®)

- **Nitrofurantoin** [nye-troe-FYOOR-an-toyn] is the ***most common* urinary tract antiseptic**.
- ***Formulations*** and ***absorption***;
    - **Nitrofurantoin Monohydrate**; ***well*** **absorbed** (***higher*** **dissolution**); ***more*** **GI distress**.
    - **Nitrofurantoin Macrocrystals** (Uvamin® retard & Macrodantin®) **absorbed *more* slowly** (***slower*** **dissolution**); ***less*** **GI distress**; **4 *times* daily**.
    - **75 mg Monohydrate + 25 mg Macrocrystal *formulation*** (Macrobid® 100); ***twice*** **daily**.
- ***Metabolism*** and ***excretion***; It is **metabolized** and **excreted *rapidly*** (***no systemic*** **antibacterial action**).
- ***Mechanism***; is ***unique*** and ***complex*** (*not fully understood*).
- ***Spectrum of activity***;
    - **Nitrofurantoin** is **bactericidal** for ***many*** **Gram +ve** and **Gram -ve *bacteria***; such as ***Escherichia coli***, ***Staphylococcus saprophyticus***, ***Enterobacter*** **species**, ***Klebsiella*** **species** and ***Staphylococcus aureus***.
    - ***Pseudomonas aeruginosa*** and *many strains* of ***Proteus*** and *some* of ***Klebsiella*** are ***inherently*** **resistant** to **Nitrofurantoin**.
- ***Doses***; ***Take*** with **food** or **milk** to ***improve*** **absorption** and ***decrease*** **GI distress**.
    - **Macrocrystals**; 50-100 mg orally every 6 hours for 7 days or for 3 days after obtaining sterile urine.
    - **Monohydrate/Macrocrystals**; 100 mg orally every 12hr for 7 days or for 3 days after obtaining sterile urine.
    - ***Children***; **>1 month-12 years** (**Macrocrystals *only***) 5-7 mg/kg/day orally divided every 6 hours for 7 days.
- ***Pregnancy***; **US FDA category B**.
- ***Contraindications*** and ***precautions***;
    - ***Significant*** **renal insufficiency** (Creatinine Clearance < 60 mL/min).
    - **Hepatic dysfunction** or **cholestatic jaundice**.
    - **Pregnancy** at term (**38-42 weeks** of ***gestation***).
    - **Neonates** (**<1 month**).
    - ***Caution*** in patients with **G6PD deficiency** (risk for hemolytic anemia).
    - ***Avoid*** **long-term use** in the **elderly** (risk for pulmonary toxicity).
- ***Side effects***;
    - ***Most common***; **GI disturbances** (**Nausea** and **vomiting**); ***Take*** with **food** or **milk**.
    - ***Rare***; **pulmonary toxicity** and **neurologic problems**.

Methenamine

- **Methenamine** [meth-EN-a-meen] or **Hexamethylenetetramine** is a **urinary tract antiseptic**, it is ***decomposes*** at an **acidic pH** of **5.5** or ***less*** in the **urine**, thus ***producing*** **Formaldehyde**, which ***acts*** **locally** and is **toxic** to **most bacteria**.

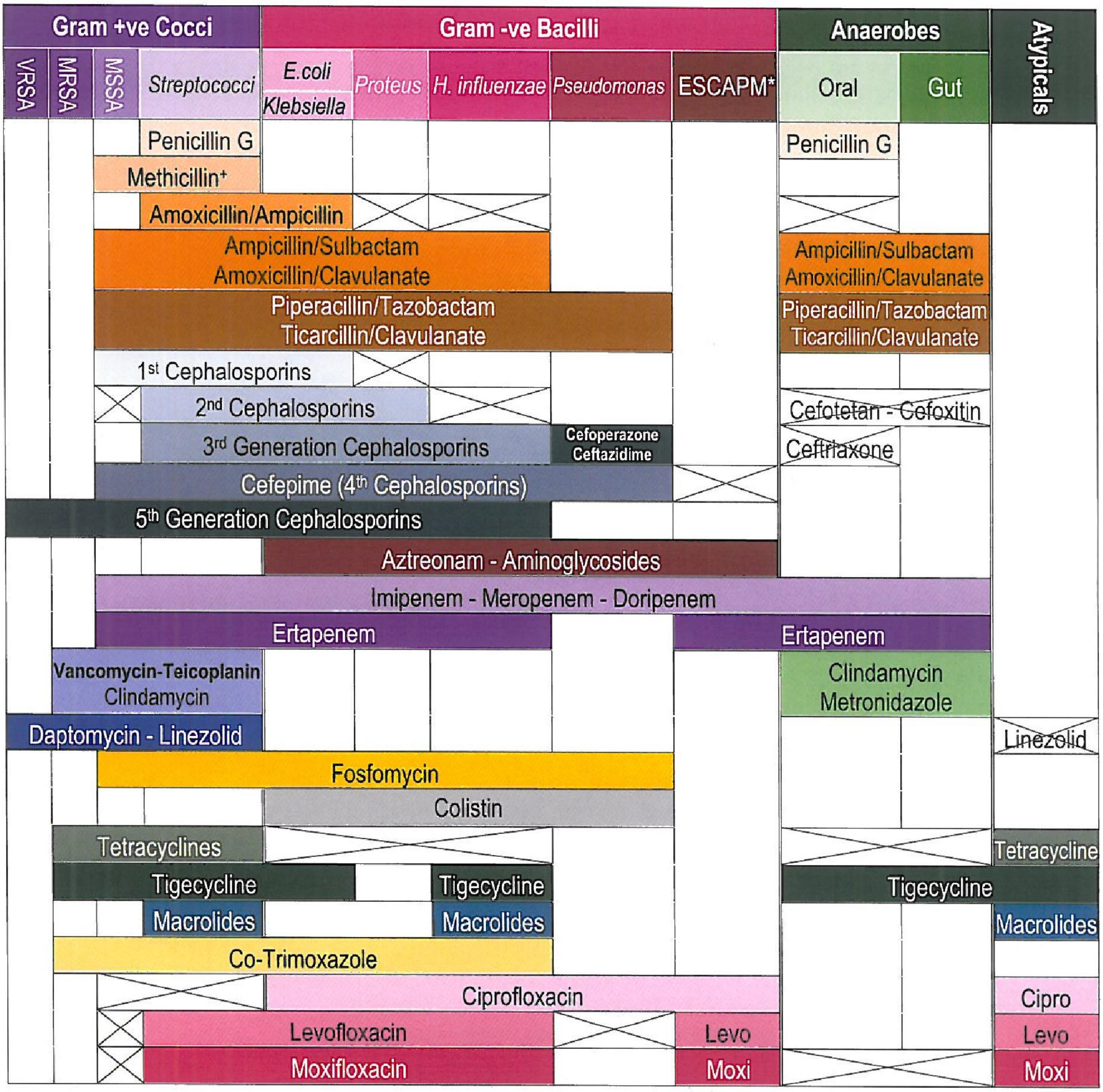


- **Bacteria *do not*** **develop *resistance*** to **Formaldehyde**, which is an ***advantage*** of this **drug**.
- ***Dose***;
    - ***Adult***; **Methenamine mandelate**; **1 g 4 *times* daily** - **Methenamine hippurate**; **1 g *twice* daily**.
    - ***Children***; **Methenamine mandelate**; 50 mg/kg/d - **Methenamine hippurate**; 30 mg/kg/d.
- **Acidifying agents** (*such as* **Ascorbic acid**; 4–12 g/d) may be **given** to ***lower*** **urinary pH *below* 5.5**.
- **Sulfonamides *should not*** be **given** at the ***same time*** *because* they ***may*** form an ***insoluble*** **compound** with the **Formaldehyde**.
- ***Side effects***; ***Most common***; **GI disturbances**.

➢ Antibiotics Classification:-

Inhibit	Classification				Antibiotics
Cell Wall Synthesis	Beta Lactams	Penicillins	Natural Penicillins		Penicillin G Penicillin V Procaine Penicillin G Benzathine Penicillin G
			Antistaphylococcal Penicillins		Methicillin Nafcillin Oxacillin Cloxacillin Dicloxacillin Flucloxacillin
			Aminopenicillins		Ampicillin Amoxicillin
			Broad Spectrum Penicillins		Ampicillin/Sulbactam Sultamicillin Co-Amoxiclav (Amoxicillin/Clavulanate)
			Anti-Pseudomonal Penicillins	Carboxypenicillins	Ticarcillin Carbenicillin
				Ureidopenicillins	Piperacillin Mezlocillin Azlocillin
				Combination	Ticarcillin/Clavulanate Piperacillin/Tazobactam
		Cephalosporins	First Generation		Cefadroxil Cephalaxin Cephradine Cefazolin
			Second Generation		Cefaclor Cefuroxime Cefprozil Cefoxitin
			Third Generation		Ceftriaxone Cefotaxime Cefoperazone Ceftazidime Ceftazidime/Avibactam Cefixime Cefdinir Cefpodoxime Cefditoren
			Fourth Generation		Cefepime Cefpirome
			Fifth Generation		Ceftobiprole Ceftaroline Ceftolozane/Tazobactam
		Monobactams			Aztreonam
		Carbapenems			Imipenem/Cilastatin Meropenem Doripenem Ertapenem
	Non-β-lactams	Glycopeptide Antibiotics			Vancomycin Teicoplanin Telavancin Dalbavancin Oritavancin
		Others			Fosfomycin Bacitracin Cycloserine
Cell Membrane					Colistin Daptomycin
Protein Synthesis Inhibitors	30S	Tetracyclines			Tetracycline Oxytetracycline Doxycycline Minocycline
		Glycylcyclines			Tigecycline
		Fluorocyclines			Eravacycline
		Aminoglycosides			Streptomycin Neomycin Amikacin Gentamicin Tobramycin
	50S	Macrolides			Erythromycin Clarithromycin Azithromycin Spiramycin Josamycin
		Ketolides			Telithromycin
		Macrocyclic			Fidaxomicin
		Chloramphenicol			Chloramphenicol
		Oxazolidinones			Linezolid Tedizolid
		Lincosamides			Clindamycin
		Streptogramins			Quinupristin/Dalfopristin Pristinamycin
	Others				Fusidic Acid Rifaximin Retapamulin Plazomicin Mupirocin
Nucleic Acid	DNA Topoisomerases	Quinolones			Nalidixic acid Cinoxacin
		Fluoroquinolones	Second		Ciprofloxacin Norfloxacin Ofloxacin Enoxacin Lomefloxacin Pefloxacin
			Third		Levofloxacin Sparfloxacin Grepafloxacin
			Fourth		Trovafloxacin Moxifloxacin Gatifloxacin Gemifloxacin
	Antifolates	Sulfonamides			Sulfamethoxazole Sulfadiazine Silver Sulfadiazine Sulfadoxine Mafenide Sulfacetamide
		DHFR inhibitor			Trimethoprim Pyrimethamine
		CO			Co-Trimoxazole Sulfadoxine/Pyrimethamine
	mRNA				Rifampicin

➢ Antibiotic Spectrum Guide:-



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<tr><th colspan="4">Gram +ve Cocci</th><th colspan="5">Gram -ve Bacilli</th><th colspan="2">Anaerobes</th><th rowspan="2">Atypicals</th></tr>
<tr><th>VRSA</th><th>MRSA</th><th>MSSA</th><th>*Streptococci*</th><th>*E.coli*
Klebsiella</th><th>*Proteus*</th><th>*H. influenzae*</th><th>*Pseudomonas*</th><th>ESCAPM*</th><th>Oral</th><th>Gut</th></tr>
<tr><td></td><td></td><td></td><td>Penicillin G</td><td></td><td></td><td></td><td></td><td></td><td>Penicillin G</td><td></td><td></td></tr>
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<tr><td></td><td></td><td></td><td colspan="2">Amoxicillin/Ampicillin</td><td>☒</td><td>☒</td><td></td><td></td><td>☒</td><td></td><td></td></tr>
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Amoxicillin/Clavulanate</td><td></td><td></td><td colspan="2">Ampicillin/Sulbactam
Amoxicillin/Clavulanate</td><td></td></tr>
<tr><td></td><td></td><td colspan="6">Piperacillin/Tazobactam
Ticarcillin/Clavulanate</td><td></td><td colspan="2">Piperacillin/Tazobactam
Ticarcillin/Clavulanate</td><td></td></tr>
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<tr><td></td><td></td><td>☒</td><td colspan="3">2nd Cephalosporins</td><td>☒</td><td></td><td></td><td colspan="2">~~Cefotetan - Cefoxitin~~</td><td></td></tr>
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Ceftazidime</td><td></td><td>~~Ceftriaxone~~</td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="6">Cefepime (4th Cephalosporins)</td><td>☒</td><td></td><td></td><td></td></tr>
<tr><td colspan="7">5th Generation Cephalosporins</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="5">Aztreonam - Aminoglycosides</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="9">Imipenem - Meropenem - Doripenem</td><td></td></tr>
<tr><td></td><td></td><td colspan="5">Ertapenem</td><td></td><td colspan="3">Ertapenem</td><td></td></tr>
<tr><td></td><td colspan="3">Vancomycin-Teicoplanin
Clindamycin</td><td></td><td></td><td></td><td></td><td></td><td colspan="2">Clindamycin
Metronidazole</td><td></td></tr>
<tr><td colspan="4">Daptomycin - Linezolid</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>~~Linezolid~~</td></tr>
<tr><td></td><td></td><td colspan="6">Fosfomycin</td><td></td><td></td><td></td><td></td></tr>
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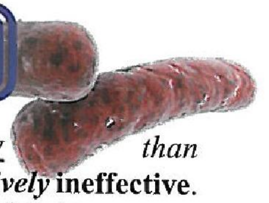
Coloured	***Good*** to ***excellent*** activity
☒	***Moderate*** activity
	Little to ***no*** activity
Methicillin^{+}	**Methicillin Group (Nafcillin - Oxicillin - Cloxacillin - Dicloxacillin - Flucloxacillin)**
ESCAPM*	*Enterobacter* spp., *Serratia* spp., *Citrobacter freundii*, *Aeromonas* spp., *Providencia* spp. and *Morganella morganii*.

➢ Topical Antibacterial Agents:-

Topical Antibacterial Agents			
Bacitracin	Polymyxin	Fusidic Acid	Mupirocin
Erythromycin	Clindamycin	Neomycin	Gentamicin
	Retapamulin	Dapsone	

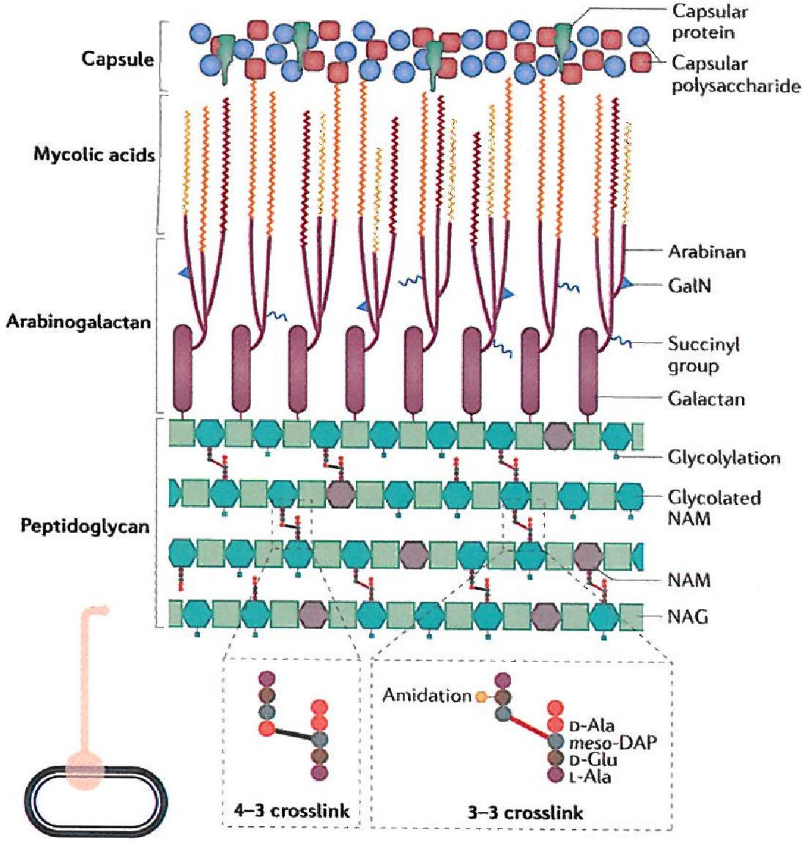
Antibiotics Fast Review

Antimycobacterial Drugs



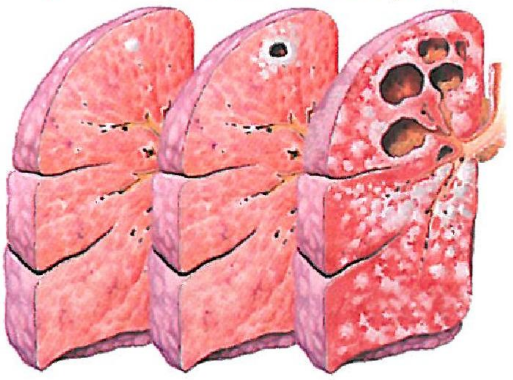
➢ **Introduction:-**

- **Mycobacteria** are ***resistant*** to ***most*** **antibiotics**; *because* they **grow *more* slowly** *than other* **bacteria, antibiotics** that are ***most active against rapidly*** **growing cells** are ***relatively*** **ineffective.**
- **Mycobacterial infections** ***classically*** **result** in the ***formation*** of ***slow growing***, **granulomatous lesions** that ***cause*** **tissue destruction** *anywhere* in the **body**.
- **Mycobacteria cell walls** contain **mycolic acids**, which give the ***genus*** its **name**.
- **Mycolic acids** are ***very*** **long-chain, β-hydroxylated fatty acids.**
- **Mycobacteria** are ***called*** "**acid-fast bacilli**" *because* they produce ***highly*** **lipophilic cell walls** that **stain *poorly*** with **Gram stain** and the **bacilli** are ***not*** **decolorized** *easily* by **acidified** *organic* **solvents.**



- **Antimycobacterial drugs** are used for the ***treatment*** of **mycobacterial infections**, ***including*** **tuberculosis** (***Mycobacterium tuberculosis***), **leprosy** (***Mycobacterium leprae***) and ***non*tuberculous mycobacteria** (These species include; ***Mycobacterium avium*** **complex (MAC)** [***Mycobacterium avium-intracellulare***], ***Mycobacterium chelonae***, ***Mycobacterium abscessus***, ***Mycobacterium kansasii***, and ***Mycobacterium fortuitum***).
- **Pharmacotherapy** of **Mycobacterial infections** is **complex**.
- **Combinations** of **drugs** are ***always*** **given** for **patients** with ***active*** **disease** to ***minimize*** the **development** of **resistance** and ***shorten*** the **duration** of **therapy**.

Anti-Tubercular Drugs



- **Tuberculosis (TB)** is an **infectious disease** *caused by* the **bacterium** ***Mycobacterium tuberculosis*** **(MTB)**.
- **TB** is a ***multi-systemic*** **disease** affects ***mainly*** the **lungs**, ***but*** can also ***affect*** *other* **parts** of the **body**.
- **TB** is the ***most*** **common *cause*** of **infectious disease–related mortality *worldwide***, *over* **2 billion *people*** *already* have been **infected (One-third "1 in 3" of the world's population)**.
- The **5 countries** with the ***highest*** **number** of incident cases in 2010 were **India, China, South Africa, Indonesia** and **Pakistan**.
- The **classic symptoms** of ***active*** TB are a ***chronic*** **cough** with ***blood-containing*** **sputum, fever, night sweats & weight loss**.
- **TB treatment *generally*** includes **4 *first-line* drugs**.
- **Second-line drugs** are *typically* ***less*** **effective, *more* toxic,** and ***less*** **extensively studied** and used for **patients** who ***cannot*** **tolerate** the ***first-line*** **drugs** or **who** are ***infected*** with ***resistant*** **TB.**
- **TB** is ***spread*** **only** from a **person** with ***active*** **TB disease** *through* **air** *when* **people cough, spit, speak** or **sneeze.**
- ***Mycobacterium tuberculosis*** is ***slow*** **growing** and ***requires*** **treatment** for **months** to **years.**

First-line

- **Isoniazid**, **Rifampin** [or **Rifampicin**] (or other **Rifamycins**), **Pyrazinamide** & **Ethambutol** are the **4** ***first-line*** **agents**. **Rifampicin** and **Isoniazid** are the ***most*** **active drugs**.

1) Rifamycins (RIF)

- **Rifamycins** are a ***group*** of **antibiotics** *includes*; **Rifamycin**, **Rifampicin** (or **Rifampin**), **Rifabutin**, **Rifapentine**, **Rifalazil** and **Rifaximin**.
- **Rifaximin** is ***not*** **used** for **mycobacterial diseases** and **used** to treat **traveler's diarrhea**, **irritable bowel syndrome** and **hepatic encephalopathy** (it has ***poor*** **oral absorption**).
- **Rifamycins** are **protein synthesis inhibitors** that ***inhibit*** **transcription** of **DNA** to ***bacterial*** **RNA**.
- **Rifamycins** are ***potent*** **CYP450 inducers**, and ***should*** always be ***screened for*** **drug interactions**.
- **Rifamycins** are **structurally** ***similar*** **macrocyclic antibiotics**.
- **Rifampicin** (or **Rifampin**), **Rifabutin** and **Rifapentine** are ***first-line*** **oral agents** for **tuberculosis**.

Rifampicin (or Rifampin) (RIF) (Rimactane®)

- **Rifampicin** [ri-FAM-picin] or **Rifampin** [ri-FAM-pin] is a ***semisynthetic derivative*** of **Rifamycin**, an antibiotic produced by ***Streptomyces mediterranei***, is the ***most commonly*** used **Rifamycins**.
- It is ***never*** **given** as a ***single*** **agent** in the *treatment of* **active tuberculosis**, ***because*** **resistant strains** ***rapidly*** **emerge** *during* **monotherapy**.
- ***Pharmacokinetics***; - ***Absorption***; ***well*** **absorbed** *after* **oral administration**.
  - ***Distribution***; ***highly*** **lipophilic**; **all body fluids** (*including* **CSF**) and **organs**.
  - ***Metabolism***; ***by*** **liver** (*undergoes* **enterohepatic recirculation**).
  - ***Excretion***: **Feces** (60-65%) and **urine** (~30%).
- **Rifampicin** is ***potent*** **CYP450 inducer**, ***leading*** to ***numerous*** **drug** **interactions**.
- ***Spectrum***; **Rifampicin** is **active** ***against*** **Gram +ve** and **Gram -ve cocci**, some ***enteric*** **bacteria**, **Mycobacteria**, and **Chlamydiae**.
- ***Mechanism***; **Rifampicin** ***binds*** to the **β subunit** of ***bacterial*** **DNA-dependent RNA polymerase** and thereby ***inhibits*** **RNA synthesis**.
- ***Resistance***; ***mutations*** in *rpoB*, the **gene** for the **β subunit** of **RNA polymerase** (there is ***no*** **cross-resistance** to ***other*** **classes** of **antimicrobial drugs**, but there is ***cross-resistance*** to ***other*** **rifamycin derivatives**, e.g., **Rifabutin** and **Rifapentine**).
- ***Uses***; - **Mycobacterial Infections**; **10 mg/kg/day** ***orally*** OR **10 mg/kg** ***orally*** **twice weekly** (*usually* 600 mg/d; not to exceed 600 mg/day), ***must*** ***be*** **administered** *with* **Isoniazid** or ***other*** **antituberculous drugs** to **patients** with **active tuberculosis** to ***prevent*** **emergence** of **drug-resistant mycobacteria**.
  - **Neisseria Meningitidis Carrier**; 600 mg twice daily for 2 days.
  - **Haemophilus Influenzae *Type B* Infection Prophylaxis**; 600 mg/day orally/IV for 4 days.
- ***Side Effects***; - **Nausea**, **vomiting** and **rash** are the ***most common***.
  - **Orange-red** ***discoloration*** *of* **urine**.
  - **Hepatotoxicity** (transient abnormalities in liver function tests) and **Jaundice**; ***incidence*** of **hepatic dysfunction** ***increased*** when **Rifampicin** is co-administered with **Isoniazid**.
  - **Flu-like symptoms**, **acute renal failure**, **hemolytic anemia**, **thrombocytopenia** and **shock** *may occur* in ***high*** **doses**.
- ***Drug Interactions***; **Rifampicin** is a ***potent*** **liver microsomal enzyme** ***inducer***; ***increase*** **metabolism** of **other drugs**, ***leading*** to ***numerous*** **drug** **interactions**.
- ***Pregnancy***; **FDA category C**; **potential benefit** should ***outweigh*** the **potential risk**.

Rifabutin (Mycobutin®)

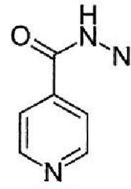
- **Rifabutin** [rif-a-BYOO-tin] is ***preferred for*** **Mycobacterium avium complex** (**MAC**).
- **MAC** *infections* are ***most*** **common** in **patients** ***with*** **human immunodeficiency virus** (**HIV**), who are often taking **antiretroviral therapy** that is ***metabolized by*** **CYP450**. ***Because*** **Rifabutin** ***less-potent*** **CYP450 inducer** ***than*** **Rifampicin**; **Rifabutin** is usually ***preferred*** in **MAC**.
- ***Side effects***; ***Like*** **Rifampicin** **but** can also *cause* **neutropenia**.

Rifapentine (Priftin®)

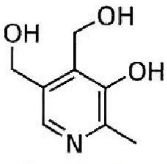
- **Rifapentine** [rih-fa-PEN-teen] has **activity** ***greater than*** **Rifampicin**, and it also has a ***longer*** **half-life**, *may be* ***used*** **once** ***weekly***.
- ***Side effects***; ***Like other*** **Rifamycins** **but** can also *cause* **hyperuricemia**.

2) Isoniazid (INH)

Isoniazid (INH)



INH



Pyridoxine

- **Isoniazid** [eye-so-NYE-a-zid], *also known as* **Iso-Nicotinyl-Hydrazide** (**INH**), *along with* **Rifampicin**, is **one** of the **two** ***most important*** **TB drugs**.
- The **structural *similarity*** to **pyridoxine** (**Vitamin B6**).
- It is ***never*** **given** as a ***single*** **agent** in the *treatment of* **active tuberculosis**, ***because*** **resistant strains** ***rapidly*** **emerge** *during* **monotherapy**.
- **Isoniazid** is a ***drug of choice*** for the **treatment** of **latent tuberculosis**; It can be given as **monotherapy** for latent (NOT Active) disease.
- *Pharmacokinetics*; - *Absorption*; ***Rapid*** **and** ***complete*** **absorption** (slowed with high-fat meals).
  - *Distribution*; **all body fluids** (*including* **CSF**) and **organs**.
  - *Metabolism*; ***by*** **liver** (*by* **acetylation**).
  - *Excretion*: ***mainly*** in the **urine**.
  - *Half-life* **elimination**; ***Pharmacogenomic metabolism***;
    - ***Fast*** **acetylators**: **30-100 min.**
    - ***Slow*** **acetylators**: **2-5 hrs.**
- The proportion of fast acetylators is higher among people of Asian origin (and Native Americans) than those of European or African origin.
- Fast acetylators may require higher dosage than slow acetylators for equivalent therapeutic effects.
- *Spectrum*; **Isoniazid** is **active** ***only*** **against** ***Mycobacterium tuberculosis*** and ***Mycobacterium kansasii***.
- *Mechanism*; **Isoniazid** ***prevents*** the **synthesis** of **mycolic acids** in the **cell wall** by ***inhibiting*** **enzymes** that *catalyze their* **production**;
  - Isoniazid is a prodrug activated by a mycobacterial catalase–peroxidase (KatG).
  - Isoniazid targets the enzymes acyl carrier protein reductase (InhA) and β-ketoacyl-ACP synthase (KasA), which are essential for the synthesis of mycolic acid.
- *Resistance*; 1) ***Mutation*** or ***deletion*** of **catalase–peroxidase** (**KatG**).
  2) ***Mutations*** of the **acyl carrier proteins**.
  3) ***Overexpression*** of the ***target enzyme***; **acyl carrier protein reductase** (**InhA**).
- *Doses* (*according to regimen*);
  - **5 mg/kg/d** (300 mg orally once daily); Typical dose.
  - **10 mg/kg/d** (600 mg orally once daily); For serious infections or in malabsorption.
  - **15 mg/kg dose** (900 mg orally) once or twice-weekly.
- *Side effects*; - **Peripheral neuropathy** (***dose-related***); can be ***prevented*** by *administering* **25–50 mg/d** of **Pyridoxine** (**Vitamin B6**).
  - **Hepatotoxicity** (*Mild* ***increase*** **liver function tests**); ***Like other*** **Rifamycins**.
  - **GI reactions**; **Nausea**, **vomiting** and **stomach pain**.
  - **Hypersensitivity reactions**; **rashes** and **fever**.
  - **Weakness**.
- *Drug Interactions*; **Isoniazid** can ***reduce*** the **metabolism** of **Phenytoin** (**CYP450** ***inhibitor***)
- *Pregnancy*; **FDA category C**.
- **Rimactazid®**; **Rifampicin** and **Isoniazid**.

➢ Brief Comparison between Rifampicin and Isoniazid:-

	Rifampicin	Isoniazid
CYP450 System	- ***Potent*** **CYP450** ***inducer***.	- **CYP450** ***inhibitor***.
Pharmacokinetics	- **Deacetylated** by the **liver**. - *Excretion*; **feces** and **urine**.	- **Acetylated** by the **liver**. - *Excretion*; **urine**.
Spectrum	- **TB**, **Leprosy** & ***other*** **bacteria**.	- **TB** ***only***.
Mechanism	- ***inhibits*** **RNA synthesis**.	- ***inhibits*** **mycolic acids synthesis**.
Side Effects	- **Nausea**, **vomiting** and **rash**. - **Hepatotoxicity** and **Jaundice**. - **Orange-red** ***discoloration*** of **urine**.	- **Peripheral neuropathy**. - **Hepatotoxicity**. - **GI & hypersensitivity** ***reactions***.

3) Pyrazinamide (PZA)

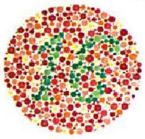
Pyrazinamide (PZA) (P.T.B®)

- **Pyrazinamide** [peer-a-ZIN-a-mide] (**PZA**) is a ***synthetic*** **relative** of **Nicotinamide**, **only used** in ***combination*** with **Isoniazid**, **Rifampin** and **Ethambutol**.
- It is ***generally*** **used** ***only*** in the ***first*** **2 months** of **tuberculosis therapy**.
- **Pyrazinamide** is ***well*** **absorbed orally**, ***widely*** **distributed** in **body tissues**, *including* **inflamed meninges** (100%); **effective** *with* **Rifampin** & **Isoniazid** in **tuberculous meningitis** (***most severe*** form).
- It is ***metabolized*** by the **liver** and its **metabolites** are ***excreted*** by the **kidneys**.
- ***Spectrum***; **Pyrazinamide** is **active** ***only*** **against** ***Mycobacterium tuberculosis***.
- ***Mechanism***; **Pyrazinamide** is a ***prodrug*** with an ***unclear*** **mechanism of action**;
  - **Pyrazinamide** is ***inactive*** (**prodrug**) at **neutral pH**, *but* ***after*** **taken up** by **macrophages** within the **acidic environment** of **lysosomes** (pH 5.5), it ***converted to*** **Pyrazinoic acid** (***active form***) by ***mycobacterial*** **pyrazinamidase**. The **specific target** of **Pyrazinoic acid** is *unknown*.
- ***Resistance***; 1) ***Impaired*** **uptake** of **Pyrazinamide**.
  2) ***Mutations*** in **Pyrazinamidase** ***enzymes***.
- ***Doses*** (*usually discontinued after* **2 months** *of a 6-month regimen*);
  - **Daily therapy**; (Non-HIV); 15-30 mg/kg orally once daily; maximum: 2 g/day.
    - **OR**; **Twice weekly Directly Observed Therapy (DOT)**; 50 mg/kg orally twice weekly; maximum: 2 g/day.
  - **HIV-exposed/infected**; 20-40 mg/kg/dose once daily; maximum: 2 g/day.
  - **Renal Dose**; (CrCl < 30 mL/min or hemodialysis); 25-35 mg/kg per dose three times per week.
- ***Side effects***; - **Hyperuricemia** and **Hepatotoxicity**.
  - **Arthralgias** (joint pains) *also occur* (separate from hyperuricemia; non-gouty).
- **N.B.**; If **hyperuricemia** is ***accompanied by*** **acute gouty arthritis**, **Pyrazinamide** ***should be*** **discontinued**.

4) Ethambutol (EMB)

Ethambutol (EMB) (Etibi®)

- **Ethambutol** [e-THAM-byoo-tole] is a ***first-line*** **drug** for the **treatment** of ***both*** **active tuberculosis** and **MAC infections** (***along with*** **Macrolides** and **Rifabutin** *for* **MAC infections**).
- **Ethambutol** ***like*** **others**, it's **used** ***only*** in ***combination*** with **Isoniazid**, **Rifampin** and **Pyrazinamide** in the *treatment of* **active tuberculosis**.
- **Ethambutol** can be **used** as a ***substitute*** for **Rifampin** in **patients** who are ***unable*** to take **Rifampin** ***during*** the **Continuation Phase** (***after*** **2 months**; intensive phase) of **active tuberculosis** ***therapy***.
- **Ethambutol** is ***well*** **absorbed orally**, ***widely*** **distributed** in **body tissues**, with ***relative*** **CSF** ***diffusion***.
- It is ***metabolized*** by the **liver** (20% to inactive) and ***excreted*** in the **urine** and **feces** as ***unchanged*** drug.
- ***Spectrum***; ***Mycobacterium tuberculosis***, ***Mycobacterium avium*** **complex** & ***Mycobacterium kansasii***.
- ***Mechanism***; **Ethambutol** ***inhibits*** **arabinosyl transferase III** ***enzyme***, which ***blocks*** *production of* **arabinogalactan** (an **essential** ***component*** of the **mycobacteria cell wall**) and **resistance** ***involves*** **alterations** in the ***emb*** **gene**.
- ***Doses***; - **Daily therapy**; 15–25 mg/kg orally once daily.
  - **Directly Observed Therapy (DOT)**; 40 mg/kg orally twice a week or 30 mg/kg orally 3 times a week.
- **Ethambutol** is ***very*** **well** ***tolerated***, ***unlike*** **others** (**Rifampin**, **Isoniazid** and **Pyrazinamide**) it's ***not associated*** with **hepatotoxicity**.
- ***Side effects***; **Optic Neuritis** *OR* **Retrobulbar Neuritis**; **Ethambutol** = **Eyes**;



  - ***Diminished*** **visual acuity**.
  - ***Loss*** of **ability** to **discriminate** ***between*** **red** & **green** (**Red-green** ***color*** **blindness**).
  - ***Not recommended*** in **children** < **5 years** old; difficult to monitor visual acuity.
  - **Vision tests** *needed for* **monitoring**.
- ***Other side effects***; **Peripheral neuropathy** and **hyperuricemia**.

Drug Regimen Example

2HREZ/4HR3

- **Rifampicin**; **RIF** or **R** - **Isoniazid**; **INH** or **H** - **Pyrazinamide**; **PZA** or **Z** - **Ethambutol**; **EMB** or **E**
- **2HREZ/4HR3**; *means*; **Isoniazid**, **Rifampicin**, **Ethambutol**, **Pyrazinamide** ***daily*** for **2 months**, *followed by* **4 months** of **Isoniazid** and **Rifampicin** given **3** ***times*** a **week**.

Second-line

- **Second-line drugs** are ***only*** **used** to **treat disease** that is ***resistant*** to **first-line therapy** (**Multi-Drug Resistant TB**; **MDR-TB**). A **drug** may be ***classed as*** **second-line**; it *may be*;
    - * ***Less effective*** than the **first-line drugs** (e.g.; ***p*-aminosalicylic acid**).
    - * ***Have*** **toxic side-effects** (e.g.; **Cycloserine**).
    - * ***Effective***, but ***unavailable*** in *many* ***developing*** **countries** (e.g.; **Fluoroquinolones**).
- **Second-line drugs** (WHO Tuberculosis Guidelines 4th edition);
    - ***Aminoglycosides***; **Streptomycin**, **Amikacin** and **Kanamycin**.
    - ***Fluoroquinolones***; **Ofloxacin**, **Levofloxacin** and **Moxifloxacin**.
    - ***Polypeptides***; **Capreomycin**.
    - ***Thioamides***; **Ethionamide** and **Prothionamide**.
    - ***Others***; ***p*-aminosalicylic acid**, **Cycloserine** and **Terizidone**.

Streptomycin

- **Streptomycin** [strep-toe-MY-sin] is an ***aminoglycoside***, was **one** of the ***first*** **effective agents** for **TB**.
- **Streptomycin** is ***no longer*** **considered** a **first-line** drug by **ATS/IDSA/CDC** *because* of ***high*** **rates** of **resistance**. American Thoracic Society (ATS) - Infectious Diseases Society of America (IDSA) - Centers for Disease Control (CDC)
- **Streptomycin** *used as* **parenterally**, ***poorly penetrates*** into **cells** and is ***active*** *mainly* ***against*** **extracellular tubercle bacilli**.
- **Infections** due to **streptomycin-resistant organisms** may be *treated with* **Amikacin** or **Kanamycin**.
- There is ***no*** **cross-resistance** ***between*** **Streptomycin** and **Amikacin**, ***but*** **Kanamycin** ***resistance*** often indicates ***resistance*** to **Amikacin** *as well*.
- ***Common side effects***; **Like** other ***Aminoglycosides***; **Ototoxicity** and **Nephrotoxicity**.

p-aminosalicylic acid

- ***Para*-aminosalicylic acid** (**PAS**) [a-mee-noesal-i-SIL-ik] was ***another*** **one** of the ***original*** **TB medications**, **PAS** is a ***folate synthesis antagonist*** (*structurally similar* to **p-aminobenzoic acid**; **PABA**).
- *From* early 1950s until well into the 1960s; **Isoniazid** + **PAS** + **streptomycin** was the ***standard*** **18-month** ***treatment*** **regimen**.
- ***Common side effects***; **GI disturbance**, **Hypersensitivity reactions** (*including* **Hepatitis**) & **Crystalluria**.

Capreomycin (Capastat®)

- **Capreomycin** [kap-ree-oh-MYE-sin] is a ***Polypeptide*** **synthesis inhibitor antibiotic**.
- **Streptomycin** or **Amikacin**-***resistant*** **organisms** may be *treated with* **injectable Capreomycin**.
- **Capreomycin** is **Nephrotoxic** and **Ototoxic**.

Cycloserine

- **Cycloserine** [sigh-kloe-SER-een] is a **cell wall synthesis** ***inhibitor***.
- **Cycloserine** is **orally effective** ***against many*** **Gram +ve** and **Gram -ve bacteria**, ***but*** it is ***used*** **ONLY** as a ***second line*** in treat **tuberculosis**.
- ***Common side effects***; **CNS toxicity** (**headaches**, **tremors**, ***acute*** **psychosis** and **convulsions**).

Ethionamide (Trecator®)

- **Ethionamide** [e-thye-ON-am-ide] is a ***structural analog*** of **Isoniazid** that also ***disrupts*** **mycolic acid synthesis**. It is **well** ***absorbed*** **orally**.
- ***Common side effects***; **GI disturbance**, **Hepatotoxicity** and **Neurologic symptoms**.

Bedaquiline (Sirturo®)

- **Bedaquiline** [bed-AK-wi-leen] is the **first** in a ***new class***; **ATP synthase** ***inhibitor*** of **mycobacteria**.
- **Bedaquiline** was **approved** in **2012** for the ***treatment of*** **Multi-Drug Resistant TB** (**MDR-TB**).
- ***Common side effects***; **QT interval prolongation**.
- ***Drug Interactions***; ***should not be*** **co-administered** with ***other*** **drugs** that are **strong** ***inducers*** (**Rifampin**) or ***inhibitors*** (**Ketoconazole**) of **CYP3A4**.

Third-line

- **Third-line drugs** are drugs that ***may be*** **useful**, ***but*** have **doubtful** or **unproven** ***efficacy***:
- **Third-line drugs** (WHO Tuberculosis Guidelines 4th edition);
    - **Clofazimine**, **Linezolid**, **Amoxicillin/clavulanate**, **Thioacetazone**, **Imipenem/cilastatin**, *high-dose* **Isoniazid** and **Clarithromycin**.

Anti-Lepral Drugs

- **Leprosy**, *also known as* **Hansen's disease**, is a ***chronic*** **infectious disease** caused by ***Mycobacterium leprae***.
- ***M. leprae*** **multiplies** ***slowly*** and ***incubation*** **period** of the **disease**, on ***average***, is **5 years**. *In some cases*; **symptoms** may *occur* ***within*** **1 year** but can also take as ***long as*** **20 years** to ***occur***.
- **Leprosy** ***mainly*** **affects**; **skin**, **peripheral nerves**, **mucosa** of **upper respiratory tract**, and *also* **eyes**.
- Although ***not highly*** **infectious**, **leprosy** is ***transmitted*** *via* **droplets**, from **nose** and **mouth**, *during* ***frequent*** **contacts** with ***untreated*** **cases**.
- This may **result** in a ***lack*** of **ability** to ***feel*** **pain**, thus ***loss*** of **parts** of **extremities** due to ***repeated*** **injuries** or **infection**.

A 24-year-old man with leprosy (1886)

- ***Prevalence***; **< 1 case** ***per*** **10,000** ***persons*** was achieved globally in the **year 2000**. ***More than*** **16** ***million*** **leprosy patients** have been **treated** with **multidrug therapy** (**MDT**) over the ***past*** **20 years**.

  As of **2013**, **14 countries** contain **95%** of the **globally** *reported* **leprosy cases**. Of these, **India** has the ***greatest number*** of cases (59%), followed by **Brazil** (14%) and **Indonesia** (8%).
- **Leprosy** can be **treated** ***effectively*** with **Dapsone**, **Rifampicin** and **Clofazimine**.

Dapsone

- **Dapsone** [DAP-sone] (**Di-amino di-phenyl sulfone**) is **structurally** ***related to*** the **sulfonamides** and **similarly** ***inhibits*** **dihydropteroate synthetase** in the **folate synthesis** ***pathway***.
- **Dapsone** used in ***combination*** *with* **Rifampicin** and **Clofazimine** for the ***treatment of*** **leprosy**.
- **Dapsone** may also be **used** to ***prevent*** and ***treat Pneumocystis jiroveci*** **pneumonia** *in* **AIDS patients**.
- ***Other Uses***; **Dermatitis Herpetiformis** and **Toxoplasmosis**.
- **Dapsone** is ***well*** **absorbed orally**, ***widely*** **distributed** in **body tissues**, with ***high*** **concentrations** in the **skin**, it is ***metabolized*** by the **liver** (*via* **CYP450**) and ***excreted*** in the **urine**.
- ***Usual adult*** **dosage** in **leprosy**; **100 mg** ***daily*** in ***combination with*** other **antileprosy drugs**.
- ***Common side effects***; **Hemolysis** (*particularly* with **glucose-6-phosphate dehydrogenase** *deficiency* patients) and **Methemoglobinemia**.

Rifampicin

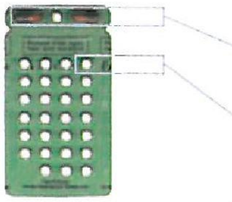
- **Rifampicin** (*see previous topic*) is **only** ***given*** in ***combination*** in a **single** **monthly** ***dose*** of **600 mg** in **adult** ***with*** **Dapsone** and **Clofazimine**.

Clofazimine (Lamprene®)

- **Clofazimine** [kloe-FAZ-i-meen] is a ***phenazine dye***, *works by* ***binding*** to **bacterial DNA**, ***inhibiting*** **bacterial** ***proliferation***.
- It is **used** ***for***;
  - **Dapsone-sensitive leprosy**; **50 mg orally daily** in ***combination*** *with* **Dapsone** and **Rifampicin**.
  - **Dapsone-resistant leprosy** or when patients are ***intolerant*** to **sulfones**; **100 mg** ***orally*** **daily** in ***combination*** *with* **1** or ***more*** other **antileprosy drugs**.
- **Clofazimine** has some **anti-inflammatory** and **anti-immune** ***activities***, thus, **erythema nodosum leprosum** *may* ***not develop*** in **patients** ***treated*** *with* ***this*** **drug**.
- ***Common side effects***;
  - **Skin discoloration** *ranging from* **red-brown** to ***nearly*** **black** (75-100%).
  - **GI intolerance**; **Nausea**, **vomiting** and **stomach pain** (40-50%).
  - **Ichthyosis** and **dry skin** (8-28%).

Drug Regimen Example

- **MDT-Combi® packs**; *donated by* **Novartis** for **WHO Multi-Drug Therapy** (**MDT**) ***regimens*** for **Leprosy**.
- *Each* **blister** of **MDT-Combi® pack** ***contains*** *treatment for* **4 weeks**, *For example* **Adult packs**;



PB adult blister pack

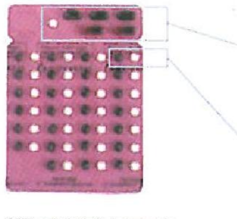
PB adult treatment:

Once a month: Day 1
– 2 capsules of rifampicin (300 mg X 2)
– 1 tablet of dapsone (100 mg)

Once a day: Days 2–28
– 1 tablet of dapsone (100 mg)

Full course: 6 blister packs

Paucibacillary leprosy (PB)



MB adult blister pack

MB adult treatment:

Once a month: Day 1
– 2 capsules of rifampicin (300 mg X 2)
– 3 capsules of clofazimine (100mg X 3)
– 1 tablet of dapsone (100 mg)

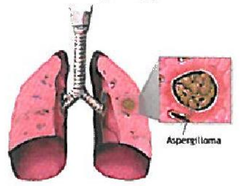
Once a day: Days 2–28
– 1 capsule of clofazimine (50 mg)
– 1 tablet of dapsone (100 mg)

Full course: 12 blister packs

Multibacillary Leprosy (MB)

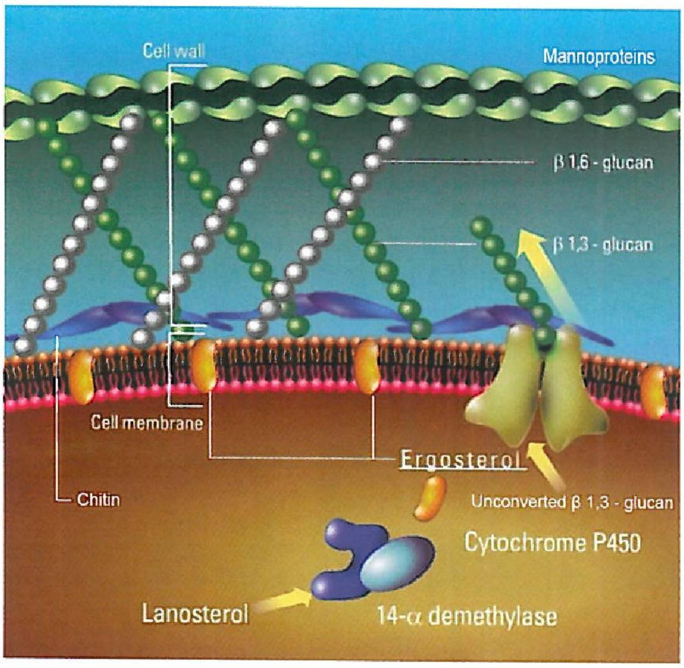
Antifungal Drugs

- **Infectious diseases** ***caused by*** **fungi** (**fungal infections** or **mycotic infections** or **mycoses**); are ***often*** **chronic** in **nature** and **many** of **mycoses** are **superficial** (*involve only* **outer layers** of the **skin** and **hair** , such as **Tinea versicolor**), while **others** ***may penetrate*** the **skin**, causing;
  - **Cutaneous** (**epidermis** and **nail**); *such as* **Tinea** (**ringworm**).
  - **Subcutaneous** (**dermis, subcutaneous tissues, muscle** and **fascia**); *such as* Debridement.
  - **Systemic infections** (*primarily* **lungs** and *may* other **organ systems**); *such as* Aspergillosis.

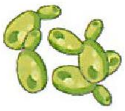
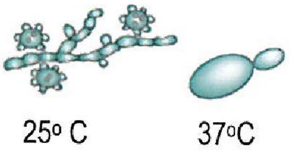
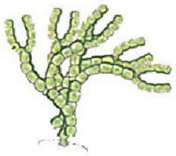


Pulmonary Aspergilloma

- ***Serious systemic fungal infections*** ***less common*** **but** ***more serious*** and *increased* **incidence** in ***patients with chronic* immune suppression *due to*** **organ transplantation, cancer chemotherapy** or infection with **human immunodeficiency virus** (**HIV**); such as **aspergillosis, fungal endocarditis** and **fungal meningitis** (**cryptococcal meningitis**).
- ***Unlike Bacteria***;
  - **Fungi** are **eukaryotic**, with ***rigid*** **cell walls** *composed largely* of **Chitin** ***rather than*** **peptidoglycan**.
  - **Fungal cell membrane** *contains* **Ergosterol** *rather than* the **cholesterol** *found in* **mammalian membranes**.
  - **Cytochrome P450** (**CYP450**) enzyme (***C-14 α-demethylase***) in **fungal cell** *responsible for* ***demethylation*** of **Lanosterol** *to* **Ergosterol**.
  - **Fungal infections** are *generally* ***resistant to*** **antibiotics**, and *conversely*, **bacteria** are ***resistant to*** **antifungal agents**.



- **Fungi**;
  - ***More than*** **70,000 species** of **fungi** have been **identified**.
  - **Microscopic fungi** *exist* in **two basic** ***forms***; **Yeasts** (unicellular) and **Molds** (multicellular).
  - **Dimorphic fungi** that **can** ***exist*** in ***either*** (**Yeasts/Molds**) **form**;
    - **Mold*-like*** at **room** ***temperature***; **Mold** *in the* **Cold**.
    - **Yeast*-like*** at **body** ***temperature***; **Yeast** *in the* **Heat**.

	Yeasts	Dimorphic	Molds
Shape		 25° C 37°C	
Common Pathogen	*Candida* *Cryptococcus*	*Histoplasma* *Blastomyces* *Coccidioides* *Paracoccidioides*	*Aspergillus* *Fusarium* *Scedosporium* *Mucorales*
Infection	Common *nosocomial bloodstream infections*	Mild, self-limited but can be fatal in immunocompromised	Common invasive disease in immunocompromised

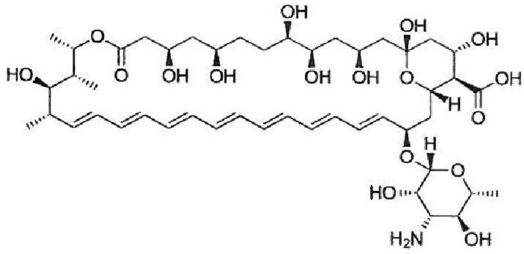
- **Antifungal agents** or **Antimycotic agents** are **fungicide** or **fungistatic** ***used to treat*** and ***prevent*** **mycoses** such as; **athlete's foot, ringworm, candidiasis** (***thrush***), **serious systemic infections.**

Systemic Antifungal for Systemic Infections

Polyene Antifungals

Amphotericin B (Fungizone®) (AmBisome®)

- **Amphotericin** [am-foe-TER-i-sin] **A** and **B** are ***antifungal antibiotics*** produced by *Streptomyces nodosus* in **1955**. **Amphotericin A** is ***not*** in **clinical use**.

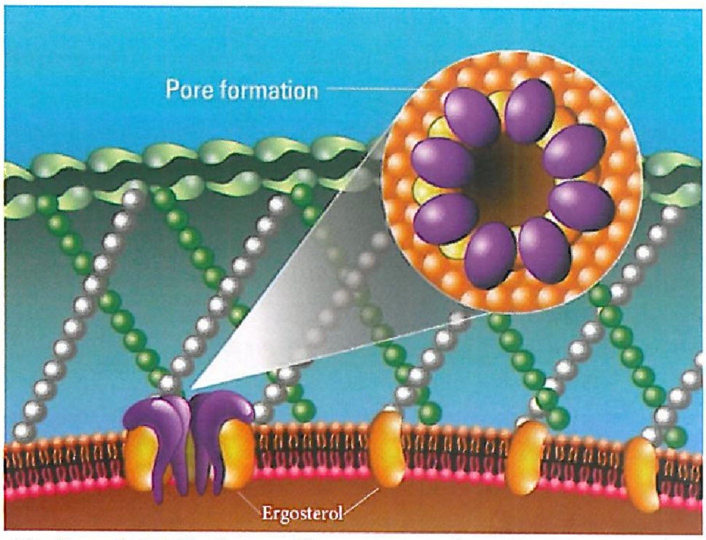


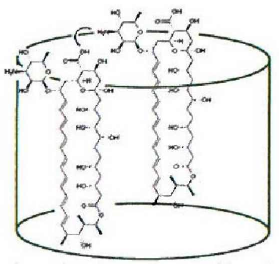
- **Amphotericin B** ***remains*** the **drug of choice** for the *treatment of* ***several*** **life-threatening mycoses** (***broad*** **antifungal** ***spectrum*** and a **lack** of *available* **alternatives**).
- **Amphotericin B** is an ***amphoteric*** **polyene macrolide**;
  - **Amphoteric** = **Can** ***act*** *both* as an **acid** as well as a **base**.
  - **Polyene** = ***Containing*** many **double bonds**.
  - **Macrolide** = ***Containing*** a **large lactone ring** of > **12 atoms**.

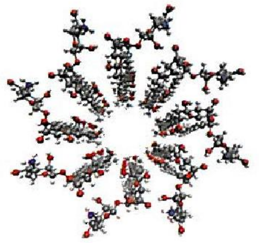
Pharmaco Kinetics

- ***Formulations***;
  - **Amphotericin B** is *nearly* ***insoluble*** in **water** and it *have* **renal** & **infusion toxicity**, therefore ***prepared*** in a ***several*** **formulations**; to ***improve*** **tolerability** and ***decrease*** **toxicity**, *but* may *show* ***different*** **pharmacokinetic characteristics** *compared to* **Conventional Amphotericin B**;
    - **Amphotericin B Sodium Deoxycholate** (**ABD**).
    - **Amphotericin B Colloidal Dispersion** (**ABCD**).
    - **Amphotericin B Lipid Complex** (**ABLC**).
    - **Liposomal Amphotericin B** (**LAmB**); ***high*** **cost**.
- ***Absorption***; ***Poorly absorbed*** **orally**, **effective** ***only*** **locally** on **fungi** ***within*** the **GIT**.
  - ***Recently*** (2011); **AmbiOnp**; a ***novel*** **solid lipid nanoparticles** of **Amphotericin B** were ***formulated*** for **oral administration** for ***systemic*** **infections**.
- ***Protein Bound***: **90%**.
- ***Distribution***; ***widely*** **distributed** in **most tissues**, but ***little*** **amount** *reached in* **CSF**.
- ***Excretion***; ***slowly*** in the **urine** ***over*** a **period** of ***several*** **days** (elimination half-life: 15 days).

- ***Mechanism***;
  - **Amphotericin B** ***binds*** to **ergosterol** ***forming*** **pores** in the **cell membrane**.
  - The **pores** ***disrupt*** **membrane** ***function***, allowing **electrolytes** (*particularly* **potassium**) and **small molecules** to ***leak*** from the **cell**, ***resulting in*** **cell death**.







- ***Antifungal spectrum***; **Amphotericin B** in ***general*** is **fungicidal**; ***depending*** on **organism** & **concentration**.
  - It is ***broad*** **antifungal spectrum**; ***Candida albicans***, ***Histoplasma capsulatum***, ***Cryptococcus neoformans***, ***Coccidioides immitis***, ***Blastomyces dermatitidis***, and *many strains* of ***Aspergillus***.
  - It is also used in the ***treatment*** of the **protozoal** ***infection*** **leishmaniasis**.
- ***Fungal resistance***; ***Decreased*** **Ergosterol** ***content*** of the **fungal membrane**.

- ***Uses***; - ***Antifungal***; **Life-threatening mycoses**, such as **Mucormycosis**, **Cryptococcal meningitis** and *certain* **aspergillus** and **Candidal infections**.
  - ***Antiprotozoal***; **Visceral Leishmaniasis** and **Amoebic Meningoencephalitis**.
- ***Dose*** (*Usual Adult*); "Double-check that dose of amphotericin B; which formulation are using"
  - **Conventional Amphotericin B**; 0.25-1 mg/kg IV infusion (***Should not exceed*** 1.5 mg/kg/d).
  - **Liposomal Amphotericin B** (**LAmB**); 3-6 mg/kg/day IV.
- **Amphotericin B** in ***diluted*** **solutions** it is ***sensitive*** to **light** and is ***inactivated*** at *low* **pH** (***should be protected from*** **light** *during* **administration**).

Side Effects

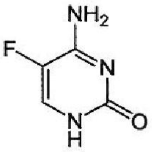
A) **Infusion-Related Reactions** (shake & bake syndrome) **Fever**, **chills**, **muscle spasms**, **vomiting**, **headache** & **hypotension**. *Can be attenuated by*;
- ***Slowing*** the **infusion rate**.
- ***Using*** **initial dosing** ***regimen***.
- ***Pre-medicating*** with **Acetaminophen**, **Hydrocortisone** and **Antihistamine**
- **Liposomal Amphotericin B** has the ***lowest*** **incidence** of ***infusion-related*** **reactions**, while **Amphotericin B Colloidal Dispersion** has the ***greatest***.

B) **Nephrotoxicity**; **Renal tubular acidosis** and ***severe*** **hypokalemia** and **hypomagnesemia** (***Caution*** when **coadministration** with other drugs that cause **hypokalemia**; e.g., **corticosteroids**, **digoxin**).
- **Renal function** *usually* **reversible**, but may be ***irreversible*** at ***high*** **doses**.
- **Azotemia** is ***exacerbated*** by *other* **nephrotoxic drugs**, such as **Aminoglycosides**, **Cyclosporine** and **Vancomycin**.
- **Liposomal Amphotericin B**, have ***less*** **nephrotoxicity** than the **Conventional Amphotericin B**.

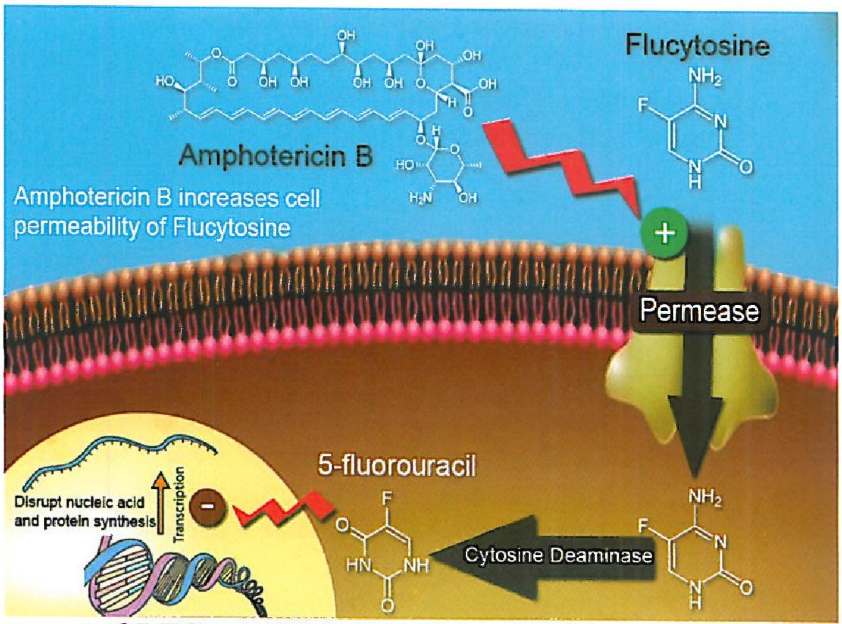
C) **Others**; **Hepatotoxicity**, **Anemia** & **Thrombophlebitis** (thrombophlebitis can decreased by adding heparin to the infusion).

Antimetabolite Antifungals

Flucytosine or 5-Fluorocytosine (Ancobon®)



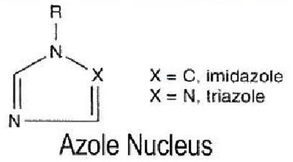
- **Flucytosine** [floo-SYE-toe-seen] or **5-Fluorocytosine** (**5-FC**) was *discovered* in **1957** *during* a **search** for ***novel*** **antineoplastic agents**, but it was ***without*** **anticancer properties**, and ***became*** apparent that it was a ***potent*** **antifungal agent**.
- **Flucytosine** is ***specifically*** **used**, *together with* **Amphotericin B**, for ***serious*** **Candida infections** and **Cryptococcosis**.
- **Flucytosine** is a ***water-soluble*** **purine** and **pyrimidine** ***analog*** *related to* the **chemotherapeutic agent 5-fluorouracil** (**5-FU**).
- ***Mechanism***;
  - **Flucytosine** ***enters*** the **fungal cell** *via* a **cytosine permease** ***enzyme*** (**not found in mammalian cells**).
  - **Flucytosine** is ***converted*** **intracellularly** ***first*** to **5-fluorouracil** (**5-FU**) and ***then*** to **5-fluorodeoxyuridine monophosphate** (**FdUMP**) and **Fluorouridine triphosphate** (**FUTP**), which ***inhibit*** **DNA**, **RNA** and **protein** ***synthesis***.
  - **Amphotericin B** ***increases*** **cell permeability**, ***allowing*** *more* **Flucytosine** to ***penetrate*** the cell and ***leading to*** synergistic **effects**.


Flucytosine
Amphotericin B
Amphotericin B increases cell permeability of Flucytosine
Permease
5-fluorouracil
Cytosine Deaminase
Disrupt nucleic acid and protein synthesis
Transcription

- ***Resistance***; ***Decreased*** **enzymes** that ***convert*** of **5-FC** to **5-FU** (*commonly* in **monotherapy**).

- ***Pharmacokinetics***;
  - ***Absorption***; ***Well* absorbed orally** (*bioavailability*; 75-90%).
  - ***Distribution***; It ***distributes*** throughout the **body fluids** and ***penetrates well*** into the **CSF**.
  - ***Metabolism***; *About* 10% by **intestinal bacteria** to **5-fluorouracil (5-FU)**.
  - ***Excretion***: **Urine** (75-90% as *unchanged* drug).
- ***Antifungal spectrum***; **Flucytosine** is **fungistatic**; it is **effective *against*** *some* **strains** of ***Candida*** and ***Cryptococcus***.
- ***Uses***; - **Flucytosine** is ***not* used** *as* a **single agent** *because* of;
  - It has **synergistic effect** with *other* **agents**.
  - To ***avoid*** the **development** of ***secondary* resistance**.
  - **Flucytosine** is **used** in ***combination*** *with*;
    - **A) Amphotericin B** for *treating* **Candidiasis** and **Cryptococcosis**.
    - **B) Itraconazole** (or **Fluconazole**) for *treating* **Chromoblastomycosis**.
- ***Dose***; **50-150 mg/kg/day orally** *divided* ***every* 6 hours**.
- ***Side effects***;
  - **GI disturbances** (**nausea**, **vomiting**, and **diarrhea**); are ***common***.
  - **Bone marrow suppression** (**anemia**, **leukopenia** and **thrombocytopenia**); *result from* ***metabolism*** of **Flucytosine** to **5-fluorouracil** by ***intestinal*** **flora**.
  - ***Reversible* hepatic dysfunction** (***elevation*** of **serum transaminases** and **alkaline phosphatase**).

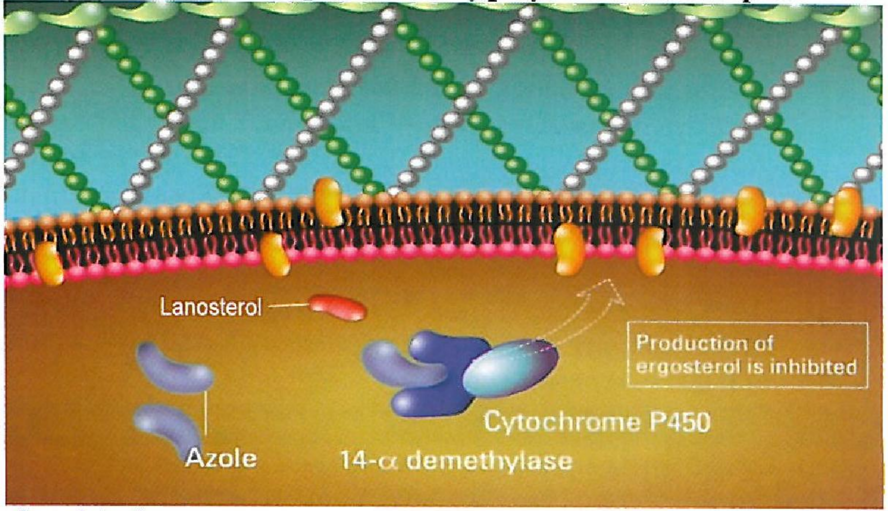
Azole (Triazole) Antifungals



Azole Nucleus

- **Azoles** are a class of ***five-membered* heterocyclic compounds *containing*** a **nitrogen *atom*** and at ***least* one** other ***non-carbon* atom** (i.e. **nitrogen**, **sulfur** or **oxygen**) as *part* of the **ring**.
- **Azoles** that are *available for* **clinical use** are ***classified as*** either **Imidazoles** or **Triazoles** ***according*** to the *number of* **nitrogen *atoms***.
- **Imidazoles** (**Ketoconazole**, **Miconazole** and **Clotrimazole**) are ***now* used *only*** in **topical *therapy***.
- **Triazoles** (**Fluconazole**, **Itraconazole**, **Posaconazole** and **Voriconazole**); are **used systemically**.
- ***Although*** **these drugs** *have* ***similar*** **mechanisms of action** and **spectra** of ***activity***, their **pharmacokinetics** and **therapeutic uses *vary* significantly**.
- **Ketoconazole** is the ***first*** **azole-*based* oral** treatment of ***systemic* fungal infections**, in the ***early* 1980s**, but ***now*** has ***largely*** been ***replaced*** due to *risk of* ***severe* liver injury**, **antiandrogenic** (**Ketoconazole** *shampoo may be beneficial* **alopecia**) and **antiglucocorticoid** and ***adverse* drug interactions**. ***Later***, **Triazoles** such as **Fluconazole** and **Itraconazole**, with ***improved*** **safety** *profile* were **developed**.

Mechanism OF Action



- ***Mechanism***; **Azoles** in ***general*** are **fungistatic**.
  - **Azoles** are ***inhibit* C-14 α-demethylase** (*a* **cytochrome P450 enzyme**), *thereby* ***blocking*** the ***demethylation*** of **Lanosterol *to* Ergosterol**, the ***principal* sterol** of **fungal membranes**.
  - The ***inhibition*** of **Ergosterol *biosynthesis*** *disrupts* **membrane *structure*** and ***function***, which, in turn, ***inhibits*** **fungal cell *growth***.
  - The ***selective*** **toxicity** of **Azoles *results*** *from* their ***greater* affinity** for **fungal *than*** for **human cytochrome P450 *enzymes***.
  - **Imidazoles** *exhibit* a ***lesser*** **degree** of ***selectivity*** *than* the **Triazoles**, ***accounting*** for their ***higher*** **incidence** of **drug interactions** and **adverse effects**.

- ***Resistance***; Specially in prolonged therapy in advanced HIV infection or bone marrow transplant;
  - ***Mutations*** in the **C-14 α-demethylase *gene*** that *lead to* ***decreased* Azoles *binding*.**
  - *Some* **strains** of **fungi** have ***developed* efflux pumps** that ***pump*** the **Azoles *out of*** the **cell.**
- ***Antifungal spectrum***; ***Broad* spectrum**, *including*;
  - *Many* **species** of ***Candida*** and ***Cryptococcus neoformans*.**
  - **Dermatophytes (endemic) mycoses (Blastomycosis, Coccidioidomycosis & Histoplasmosis).**
  - **Itraconazole** and **Voriconazole** are ***effective* against *Aspergillus* infections.**

Drug Interactions

- ***All* Azoles *inhibit*** the **hepatic CYP450 isoenzymes** (*especially* **CYP450 3A4**) to ***varying* degrees**; ***decrease* metabolism** of **other drugs**, ***leading* to *numerous* drug interactions.**
- ***Potent* CYP450 *inducers*** (e.g.; **Rifampicin**) can *lead to* ***decrease* effect** of **Azoles.**
- ***Potent* CYP450 *inhibitors*** (e.g.; **Ritonavir**) can *lead to* ***increased* adverse effects** of **Azoles.**

Fluconazole (Diflucan®)

- **Fluconazole** [floo-KON-a-zole] was the ***first* member** of the **Triazole** class of ***antifungal agents***, was ***patented by*** **Pfizer** in **1981**, and in ***early* 1990s** **Fluconazole** was a ***breakthrough*** in **antifungal pharmacotherapy.**
- **Fluconazole** is ***highly* bioavailable** (***available*** in *both* **oral** and **IV** ***formulations***), with ***fewer* hepatic enzyme *interactions*** (***least* CYP450 *effect***), with ***better* GI *tolerance*** and ***widest* therapeutic index** of ***all* Azoles.**
- ***Antifungal spectrum***; ***least* spectrum** of ***all* Triazoles** (***least* CYP450 *effect*** of ***all*** the **Azoles**);
  - ***Highly* active** *against* ***most Candida* species** (*but* **NOT** ***Candida krusei*** or ***Candida glabrata***).
  - ***Good* activity** *against* ***Cryptococcus neoformans*** (e.g.; **Cryptococcal meningitis**)
  - ***Also* active** *against some* **Dimorphic *fungi*.**
  - ***No* activity** *against* ***Aspergillus* species.**
- ***Uses***; Dose is *same* in IV and oral administration; ***highly* bioavailable.**
  - **Vulvovaginal Candidiasis; 150 mg orally** as a ***single* dose** (May repeated if complicated or recurrent)
  - **Oropharyngeal** *and* **Esophageal Candidiasis; 200 mg IV** or **orally** on the ***first* day** *followed by* **100 mg IV** or **orally *once*** a **day.**
  - **Systemic Candidiasis** *and* **Cryptococcal Meningitis; 400 mg IV** or **orally** on the ***first* day** *followed by* **200 mg IV** or **orally *once*** a **day.**
  - **Dermatomycosis** (*such as*; **tinea**); **150 mg *once weekly*** OR **50 mg *once* daily; 2-4 weeks, tinea pedis (athlete's foot)**; *may require* up to **6 weeks.**
  - **Onychomycosis (fungal nail infections); 150** to **300 mg orally *once*** a **week** (3 to 6 months).
  - ***Prophylaxis*** of **Candidiasis** with **Bone Marrow Transplantation** (BMT); **400 mg/day IV** or ***orally*.**
- ***Usual children dose***; **6-12 mg/kg** on the ***first* day** *followed by* **3-12 mg/kg/day**;
  - Duration and dosage depend on severity of infection.
- ***Side effects***;
  - ***Most common***; **headache, nausea, vomiting** and **skin rashes.**
  - **Hepatotoxicity** *can also* **occur** (***should be*** used with **caution** in *patients with* **liver dysfunction**).
  - **QT interval *prolongation*** is *also possible*.

Itraconazole (Sporanox®)

- **Itraconazole** [it-ra-KON-a-zole] is a ***second* member** of the **Triazole** class, it was ***invented*** in **1984.**
- **Itraconazole** has a ***broader* spectrum** of **activity** *than* **Fluconazole** (**BUT** ***not as*** *broad as* **Voriconazole** or **Posaconazole**); It is **active *against Aspergillus***, which **Fluconazole** is ***not***.
- **Itraconazole** is the ***drug of choice*** for; **Blastomycosis, Sporotrichosis, Histoplasmosis**, and **Onychomycosis.** It is ***rarely used*** for ***Candida*** and ***Aspergillus* species** *because* of the ***availability*** of ***newer*** and ***more* effective agents** (**Voriconazole** or **Posaconazole**).
- **Itraconazole** is ***available*** in **oral** and **IV *formulations*** (**IV *has been* discontinued** by the **manufacturer**).
- ***Oral dosage forms*** (**capsules** have ***lower* bioavailability** than **oral solution**)
  - **Oral solution**; ***should be* taken** on an **empty stomach**, as **food *decreases*** the **absorption.**
  - **Capsules**; ***should be* taken *with* food**, and ***ideally*** an **acidic beverage** (**orange juice** or **cola**) to ***increase* absorption**; **acid suppression *therapy*** like **PPIs**; ***decrease* absorption.**

- The **Sporanox®** brand of Itraconazole has been ***developed*** and ***marketed*** by **Janssen Pharmaceutica**; were **capsules** is ***discovered by*** the Korean Patent Laid-open No. 10-2001-2590.
- **Sporanox® capsules *contain*** *tiny* **1.5 mm pellets** *with* ***complex*** **three-layer structure** to ***increase*** **absorption** and **bioavailability**;
  1) **Inner layer**; Itraconazole 1 part by weight.
  2) **Mid-layer**; Citric acid 0.25 part by weight.
  3) **Outer layer**; Hydroxypropylmethylcellulose 0.25 part by weight.
- **Itraconazole** is *over* ***99% protein-bound*** and **penetrates** ***poorly*** into **CSF** (*NOT* preferred in **meningitis**)
- ***Antifungal spectrum***;
  - ***Highly*** **active** *against* ***most*** of ***Candida*** and ***Aspergillus*** **species**, ***Cryptococcus neoformans***, and ***many*** **dimorphic** fungi (**Itraconazole** is the azole of choice for dimorphic infections).
  - ***Good*** **activity** *against* ***Candida krusei*** and ***Candida glabrata***.
- ***Uses***; **Blastomycosis, Sporotrichosis, Histoplasmosis** and **Onychomycosis**.
- ***Usual dose***; - ***Adult***; 100-200 mg twice a day. - ***Children***; ≥3 years: 3-5 mg/kg/day.
- ***Side effects***; - ***Most common***; **nausea**, **vomiting** and **rash**.
  - **Hypokalemia, hypertension, edema** and **headache** are *common*.
  - **Hepatotoxicity** *can* also **occur**.
- **Black Box** - ***Negative*** **inotropic effect** *can* also **occur** (*should be* **avoided** in **patients** *with* **heart failure**).

Voriconazole (Vfend®)

- **Voriconazole** [vor-i-KON-a-zole] is ***similar*** to **Itraconazole** in its ***spectrum***, having ***excellent*** **activity** *against* ***Candida*** (*including* **Fluconazole** ***resistant*** **species** such as ***Candida krusei***), ***Cryptococcus neoformans***, ***Aspergillus***, ***Scedosporium*** and ***Fusarium*** **species** (**Voriconazole** is the **drug of choice** for **invasive aspergillosis**; *less toxic* than **Amphotericin B**), and ***many*** **dimorphic** ***fungi***.
- ***Unlike*** **Itraconazole**, **Voriconazole** is ***well*** **absorbed** and ***available*** in ***both*** ***highly*** **bioavailable oral *formulation*** and **IV admixture** (***exceeding*** 95%).
- **Voriconazole IV admixture** with **Sulfobutylether β-Cyclodextrin (SBECD)** is ***restricted*** in **patients** with **renal insufficiency** (Creatinine clearance <50 mL/min); **SBECD** ***accumulate*** in **renal dysfunction**.
- ***Uses***; **Invasive Aspergillosis, Candidemia, Esophageal Candidiasis** and **Serious Fungal Infections**.
- ***Usual dose***; **6 mg/kg IV *every* 12 hours** on **day 1**, then **4 mg/kg IV *every* 12 hours** (IV therapy should continue for at least 7 days), **oral dose 100 mg** (< 40 kg) to **200 mg** (> 40 kg) ***every* 12 hours**.
- ***Side effects***; - ***Most common***; **Visual disturbances** (Photophobia, color changes, increased or decreased visual acuity, or blurred vision occur in up to 28%).
  - ***Very common***; **Skin rashes**, **phototoxicity**, **headaches**, **peripheral edema**, **fever**, ***trouble*** **breathing**, **nausea**, **vomiting** and **diarrhea**.

Posaconazole (Noxafil®)

- **Posaconazole** [poe-sa-KONE-a-zole] is a ***broad-spectrum*** **triazole antifungal**, *structurally* ***similar*** to **Itraconazole**, that is ***more*** **active** ***against*** *many* **fungi**.
- **Posaconazole** is available as an **oral suspension**, **oral tablet** or **IV formulation**; ***absorption*** is ***improved*** when **taken** *with* ***high*** **fat meals** (*increases* **concentration** by **4 times** *compared to* **fasting** *state*); **acidic beverage** (**orange juice** or **cola**) ***increase*** **absorption**; drugs such as **PPIs** ***decrease*** **absorption**.
- **Posaconazole** is the ***broadest*** **spectrum** *member* of the **azole** family, with ***activity against most*** **species** of ***Candida***, ***Aspergillus*** and ***Zygomycetes***.
- ***Uses***; - **Invasive aspergillosis** and **candidiasis**.
  - **Oropharyngeal candidiasis (OPC)**; *including* **OPC *refractory*** to **Itraconazole** and/or **Fluconazole**.
- ***Usual dose***; **300 mg orally *twice*** a **day** on the ***first*** **day**, *then* **300 mg orally *once*** a **day**.
- ***Side effects***; ***Most common*** (> 10%); **Headache**, **fever**, **nausea**, **diarrhea**, **anemia**, **hypokalemia** and **hypomagnesemia**.

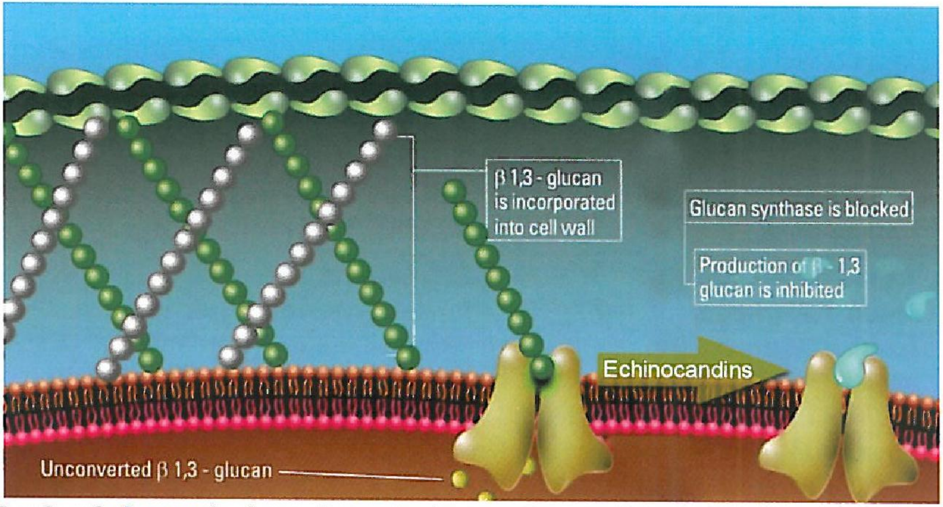
Isavuconazole (Cresemba®)

- **Isavuconazonium** [EYE-sa-vue-KOE-na-ZOE-nee-um] **sulfate** is a ***prodrug*** for **Isavuconazole**.
- **Isavuconazole** is the ***newest*** **triazole antifungal**; FDA approval in March 2015.
- It is ***available as*** **IV** and **oral** ***formulations***.
- **Isavuconazole** is ***used*** to treat **invasive aspergillosis** and **invasive mucormycosis (Zygomycosis)**.
- ***Dose***; - *Loading*; 1 vial (372 mg) IV or 2 capsules (372 mg) orally, every 8 hours for 6 doses (48 hours).
  - *Maintenance*; 1 vial (372 mg) IV or 2 capsules (372 mg) once daily.

Echinocandins

- **Echinocandins** are the ***newest*** **class** of **antifungal drugs**, **Caspofungin** was the ***first*** **drug** in this **class** to be **approved** by FDA in **2001**. **Micafungin** and **Anidulafungin** are *new* ***available*** **agents**.
- **Echinocandins** are ***large*** **cyclic peptides** *linked to* a ***long-chain*** **fatty acid**. So they are *available* ***only*** in **IV** ***formulations***.
- **Echinocandins** have ***potent*** **activity** ***against*** *Aspergillus* and ***most*** ***Candida*** **species**.
- **Echinocandins** have an ***excellent*** **safety profile**. They can cause ***mild*** **Histamine**-*mediated* **infusion**-*related* **reactions** (**flushing**).
- **Caspofungin** and **Micafungin** (***not*** **Anidulafungin**) are ***slowly*** **metabolized** ***by*** **peptide** ***hydrolysis*** and **N-acetylation** in **liver**, ***elevated*** **liver enzymes** have been ***noted***.
- **Anidulafungin** is the ***only*** **Echinocandins** can be ***administered*** in **severe hepatic dysfunction**.
- ***Co-administered*** of **Caspofungin** *with* **Cyclosporine** OR **Micafungin** *with* **Sirolimus** *carry* ***high*** **incidence** of ***elevated*** **liver enzymes**.

Mechanism OF Action


β 1,3 - glucan is incorporated into cell wall
Glucan synthase is blocked
Production of β - 1,3 glucan is inhibited
Echinocandins
Unconverted β 1,3 - glucan

- **Echinocandins** ***inhibits*** **synthesis** of **glucan** in the **cell wall**, via ***non-competitive*** **inhibition** of **1,3-β-D-glucan synthase** ***enzyme***. This results in ***disruption*** of the **fungal cell wall** and **cell death**.

Caspofungin (Cancidas®)

- **Caspofungin** [kas-poh-FUN-jin] was the ***first*** **member** of the **Echinocandins**.
- ***Uses***; - **Invasive Candidiasis**, *including* **Candidemia**; ***first line***.
  - **Invasive Aspergillosis** in **patients** ***refractory to*** or ***intolerant*** of *other* **therapies** (e.g., **Amphotericin B** or **Itraconazole**); ***second line***.
- ***Dose***; 70 mg IV infused over 1 hr in day first day, then 50 mg IV infused over 1 hr per day.
- ***Warning***; - **Hypersensitivity** and **Anaphylaxis**.
  - ***Do not*** **use** **Dextrose** ***diluents*** (**Caspofungin** is not stable).
  - ***Do not*** **use** *with* **Cyclosporine** (unless benefits outweigh risks).
  - *Not* for **bolus administration**.

Micafungin (Mycamine®) | Anidulafungin (Eraxis®)

- **Micafungin** [mi-ka-FUN-jin] and **Anidulafungin** [ay-nid-yoo-la-FUN-jin] are ***newer*** **members** of **Echinocandins**.
- ***Uses***; **Invasive Candidiasis**, *including* **Candidemia**.
- ***Dose***; - **Micafungin**; 100-150 mg/day IV infusion (is the ***only*** **echinocandin** ***not require*** a **loading dose**)
  - **Anidulafungin**; 200 mg IV infusion in first day, then 100 mg/day IV.
- *N.B.*; **Anidulafungin** is ***not*** **metabolized** by **liver** ***can be*** *administered* in **severe hepatic dysfunction**.
- ***Warning***; - **Hypersensitivity** and **Anaphylaxis**.
  - **Micafungin** ***not*** **used** *with* **Sirolimus** and **Nifedipine**.
  - *Not* for **bolus administration**.

Systemic Antifungal for Cutaneous Mycotic Infections

- **Cutaneous fungal (mycotic) infections** are ***non*-invasive infections** of the **skin**, **hair** or **nails**;
    - **Dermatophytosis (skin and hair)**;
        - **Tinea Corporis (ringworm).**
        - **Tinea Faciei (facial ringworm).**
        - **Tinea Cruris (jock itch).**
        - **Tinea Pedis (athlete's foot).**
        - **Tinea Capitis (scalp ringworm).**
        - **Tinea Manuum (ringworm of the hands).**
    - **Onychomycosis (tinea unguium); nail fungal infection.**

Onychomycosis

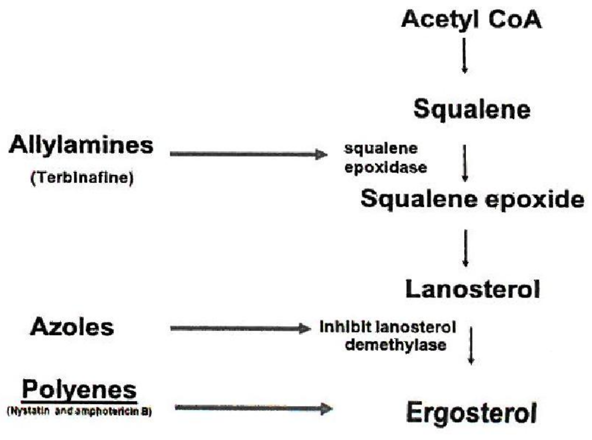
- **Cutaneous infections** are *usually* ***treated with*** **topical agents**, but ***persistent*** and ***non-responsive*** **infections** are ***better*** **treated** with **oral antifungal agents.**

Griseofulvin (Ultragriseofulvin®) (Grifulvin V®)

- **Griseofulvin** [gris-ee-oh-FUL-vin] was ***discovered*** in **1939** from ***Penicillium griseofulvum***, and it was the ***first** available* **oral agent** for the ***treatment of*** **Dermatophytosis.**
- **NOW Griseofulvin** has been ***largely*** *replaced by* **oral Terbinafine** for the ***treatment of*** **Onychomycosis**, although it is ***still used*** for **Dermatophytosis.**
- ***Pharmacokinetics***;
    - ***Formulations***; - **Microsize** OR **Ultramicrosize**; **capsules, tablets** or **suspension.**
        - **Griseofulvin** is ***ineffective*** **topically.**
    - ***Absorption***; - **Ultramicrosize Griseofulvin; absorption** is almost ***complete.***
        - **Microsize Griseofulvin; 25-70%** of **oral dose** (***enhanced by*** **fatty meal**).
        - **GI absorption** of **Ultramicrosize** is **1.5 *times*** that of **Microsize.**
    - ***Distribution***; ***concentrates*** in **skin, hair, nails** and **adipose tissue.**
    - ***Metabolism***; by the **liver** to **6-desmethylGriseofulvin** and its **glucuronide** ***conjugate.***
    - ***Excretion***; **Urine, feces** and **perspiration.**
- ***Mechanism***; **Fungistatic.**
    - *After* **oral administration, Griseofulvin** is ***deposited*** in the **keratin *precursor* cells** and has a ***greater*** **affinity *for*** **diseased tissue.**
    - **Griseofulvin** is ***tightly*** **bound** *to* the ***new*** **keratin** *forming* **keratin-Griseofulvin complex**, which *becomes* ***highly*** **resistant *to*** **fungal *invasions.***
    - ***Once*** the **keratin-Griseofulvin complex *reaches*** the **skin *site of action***, it ***binds*** to **fungal microtubules (tubulin)** thus ***altering*** **fungal *mitosis.***
- ***Dose***; 2–6 weeks for skin & hair infections (Dermatophytosis) and 4-6 months for nail infections (Onychomycosis).
    - ***Microsize***; 1000 mg/day orally in 2 to 4 divided doses.
    - ***Ultramicrosize***; 660 to 750 mg/day orally in 2 to 4 divided doses.
- ***Side effects***; **Rash, urticaria, headache, GI disturbance** and **oral thrush.**
- ***Contraindicated*** in ***patient with*** **porphyria.**

Terbinafine (Lamisil®)

- **Terbinafine** [TER-bin-a-feen] is a ***synthetic*** **Allylamine (Squalene Epoxidase Inhibitor)** that is *available in* an **oral** and **topical** ***formulations.***
- ***Mechanism***; **Fungicidal.**
    - **Allylamines** *act by* ***inhibiting*** **squalene epoxidase *enzyme***, thereby ***blocking*** the **biosynthesis** of **Ergosterol**, an ***essential*** **component** of the **fungal *cell membrane*** (not act on CYP450).
    - ***Accumulation*** of **toxic amounts** of **squalene** results in ***increased*** **membrane *permeability*** and **death** of the **fungal cell**;
- **Terbinafine** is the ***drug of choice*** for ***treating*** **Onychomycosis**; - **Better tolerated.**
    - ***Shorter*** **duration** of **therapy.**
    - ***More*** **effective.**



- ***Pharmacokinetics***;
    - ***Absorption***; > **70%**.
    - ***Protein bound***; > **99%**.
    - ***Excretion***; *mainly* via **urine**.
    - ***Bioavailability***; ***only* 40%** *due to* **first-pass *metabolism***.
    - ***Metabolism***; by *several* **CYP450 *isoenzymes***.
- ***Uses*** and ***Doses***;
    - **Onychomycosis**; 250 mg orally once daily for 6 weeks (fingernail) or 12 weeks (toenail).
    - **Tinea Corporis, Tinea Cruris**; 250 mg/day orally in single dose or divided every 12hr for 2-4 weeks.
    - **Tinea Pedis** (Off-label); 250 mg/day orally in single dose or divided every 12hr for 2-6 weeks.
    - **Sporotrichosis, Lymphocutaneous** and **Cutaneous** (Off-label); 500 mg/day PO q12hr for 2-6 weeks; treat for additional 2-4 weeks after resolution of all lesions (resolution may take 3-6 months).
- ***Pregnancy***; **Category B.**
- ***Lactating women***; ***Accumulates*** in **breast milk** and ***should not*** be *given to* **nursing mothers**.
- ***Side effects***; **Headache**, **GI disturbances** and **rash**.
- **Terbinafine** is used with ***caution*** in **renal** and **liver *impairment***.

Topical Antifungals

Polyene Antifungal

Nystatin (Mycostatin®)

- **Nystatin** [nye-STAT-in] is a ***polyene* antifungal**, and its ***structure***, ***chemistry***, ***mechanism of action***, and ***resistance profile resemble*** *those of* **Amphotericin B**.
- **Nystatin** is ***negligibly absorbed*** from **GIT**, and ***not* used *parenterally*** *due to* **systemic toxicity** (*acute* **infusion-related reactions** and **nephrotoxicity**); **Liposomal Nystatin** is also available *off-label* for **invasive fungal infections**.
- ***Uses*** and ***Doses***;
    - **Oropharyngeal Candidiasis**; - **1-12 months**; 200,000 *units* 4 *times* daily.
        - **1-18 years**; 400,000 to 600,000 *units* 4 *times* daily.
    - **Intestinal Candidiasis**;
        - **Oral tablets**: 500,000-1,000,000 *units* every 8 hours
        - **Powder**: 1/8 to 1/4 teaspoonful in 1/2 cup of water (500,000-1,000,000 units) orally every 8 hours

Azole (Imidazole) Antifungals

Ketoconazole (Nizoral®)	**Miconazole** (Daktarin®)	**Econazole** (Pevaryl®)
Isoconazole (Travocort®)	**Clotrimazole** (Canesten®)	**Oxiconazole** (Tinox®)
Tioconazole (Trosyd®)	**Sertaconazole** (Dermofix®)	**Butoconazole** (Gynazole-1®)
Sulconazole (Exelderm®)	**Terconazole** (Terazol®)	**Bifonazole** (Mycospor®)

- **Ketoconazole** [kee-toe-KON-a-zole], **Miconazole** [my-KON-a-zole], **Econazole** [e-KONE-a-zole], **Isoconazole** [eye-ess-oh-KON-a-zole], **Clotrimazole** [kloe-TRIM-a-zole], **Oxiconazole** [oks-i-KON-a-zole], **Tioconazole** [tye-oh-KONE-a-zole], **Sertaconazole** [serta-KOE-na-zole], **Butoconazole** [byoo-toe-KON-a-zole], **Sulconazole** [sul-KON-a-zole], **Terconazole** [ter-KONa-zole] and **Bifonazole** [bye-FON-a-zole] are ***imidazole derivatives***, which **currently *available***.
- ***Topical* Imidazoles** have a ***variety*** of **uses**, *including*; **tinea corporis**, **tinea cruris**, **tinea pedis** and **oropharyngeal** and **vulvovaginal candidiasis**.
- ***Side effects***; ***contact* dermatitis**, **vulvar irritation** and **edema**.

Allylamine Antifungals

Terbinafine (Lamisil®)	**Naftifine** (Exoderil®)
Butenafine (Derfina®)	**Amorolfine** (Loceryl nail lacquer®)

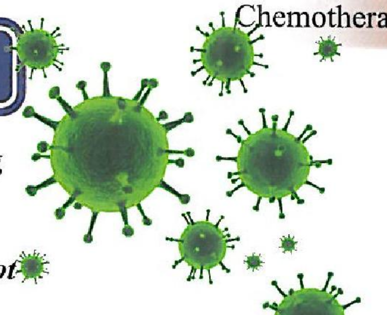
- **Terbinafine** [TER-bin-a-feen], **Naftifine** [NAF-ti-feen], **Butenafine** [byoo-TEN-a-feen] ***used for*** **topical treatment** of **tinea infections**.
- **Loceryl nail lacquer®** is a **nail solution** of **Amorolfine** *for* **fungal nail infection *once*** or ***twice* weekly**.

Others

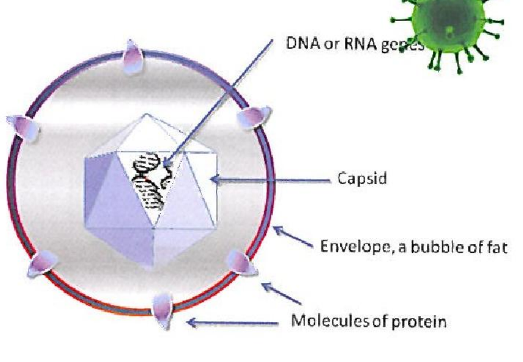
Ciclopirox (Batrafen®)	**Tolnaftate** (Tineacure®)	**Clioquinol** (Betnovate-C®)

- **Ciclopirox** [sye-kloe-PEER-oks] and **Tolnaftate** [tole-NAF-tate] are ***available*** in a *number of* ***formulations*** for **cutaneous mycotic infections**.
- **Clioquinol** [klye-oh-KWIN-all] or **Iodochlorhydroxyquin** is an ***antifungal*** and ***antiprotozoal drug***.

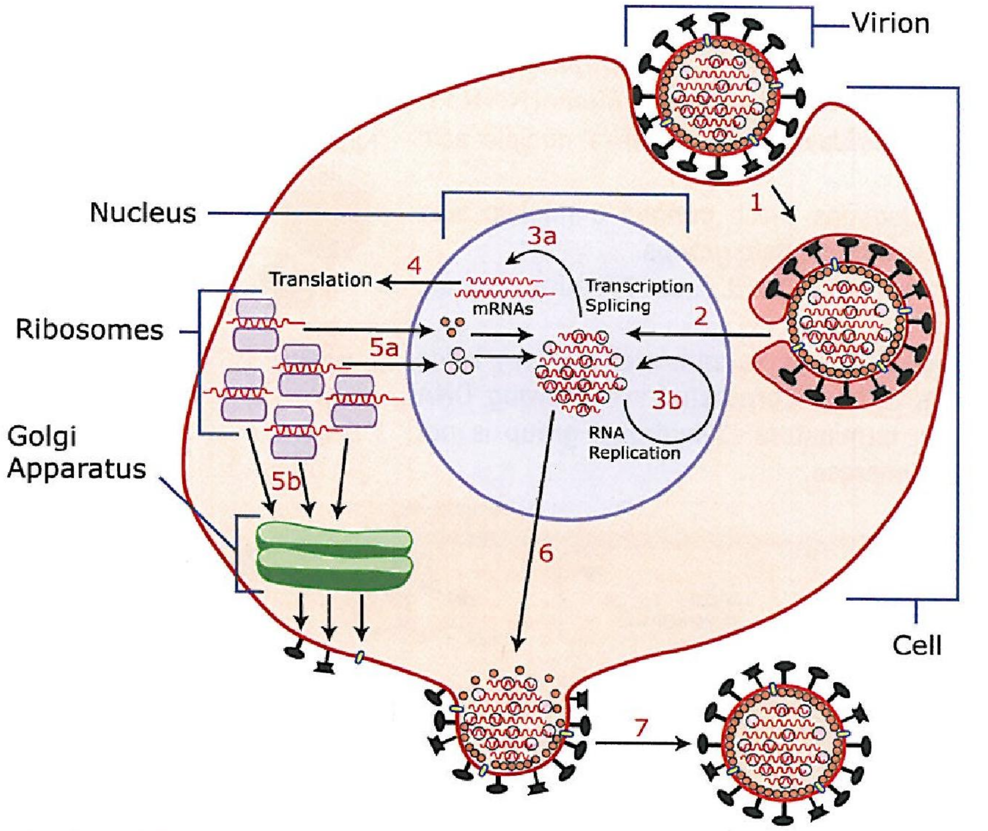
Antiviral Drugs



- **Virus** is a ***small*** **infectious agent** that **replicates** ***only inside*** the **living cells** of *other* **organisms** (***all types*** of **life forms**; from **animals** and **plants** to **microorganisms**, *including* **bacteria** and **archaea**).
- **Viruses** are ***lack*** both a **cell wall** and a **cell membrane**, and they ***do not carry out*** **metabolic processes**.
- **Viral particles** (**Virions**), *consist of* **two** or **three** ***parts***:
  1) **Genetic Material**; either DNA or RNA.
  2) **Protein Coat** (**Capsid**); which surrounds and protects the genetic material.
  3) **Envelope of Lipids** (**Envelope**); Lipid layer that surrounds the protein coat when they are outside a cell.



- **Viruses** ***cannot*** **reproduce** on ***their*** **own**, they are use **host's metabolic** ***processes***, and so a ***few*** **drugs** are ***selective*** **enough** to ***prevent*** **viral replication**.
- **Replication cycle**; The **virus replication** occurs in **7 stages**, *namely*;
  1) **Adsorption (Attachment)**, 2) **Entry**, 3) **Uncoating**,
  4) **Transcription/mRNA production**, 5) **Synthesis of virus components**, 6) **Virion assembly (Maturation)**,
  7) **Release**.

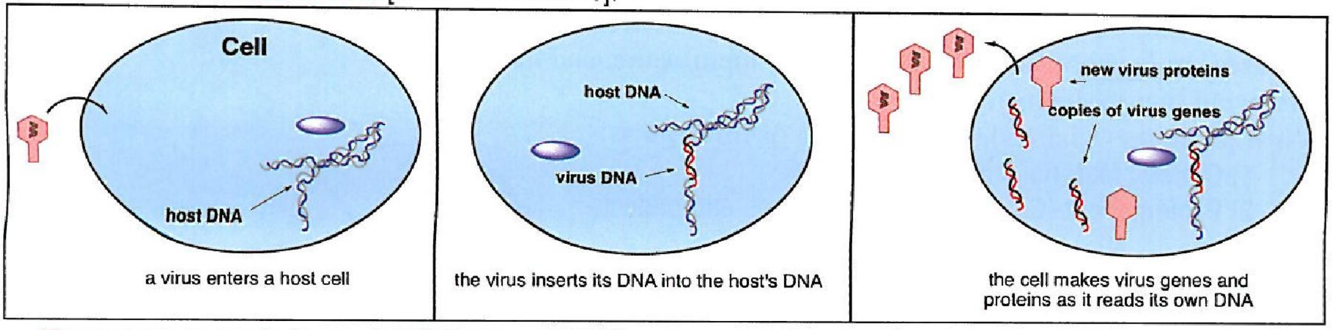


Acronyms

CMV; Cytomegalovirus
EBV; Epstein-Barr virus
HBV; Hepatitis B virus
HCV; Hepatitis C virus
HIV; Human immunodeficiency virus
HSV; Herpes simplex virus
NNRTI; Nonnucleoside reverse transcriptase inhibitor
NRTI; Nucleoside/nucleotide reverse transcriptase inhibitor
PI; Protease inhibitor
RSV; Respiratory syncytial virus
SVR; Sustained viral response
VZV; Varicella-zoster virus

- **Antiviral drugs** may ***target*** **specific steps** of **viral replication**;
  - **Viral attachment** and **entry** are *blocked by*; **Enfuvirtide** (**HIV**), **Maraviroc** (**HIV**); **Docosanol** (**HSV**) and **Palivizumab** (**RSV**).
  - **Uncoating** are *blocked by*; **Amantadine** and **Rimantadine** (**influenza**).
  - **Nucleic acid synthesis** are *blocked by*; **Nucleoside Reverse Transcriptase Inhibitors**; **NRTIs** (**HIV, HBV**), **Non-nucleoside Reverse-transcriptase Inhibitors**; **NNRTIs** (**HIV**), **Acyclovir** (**HSV**) and **Foscarnet** (**CMV**).
  - **Protein processing** are *blocked by*; **Protease Inhibitors** (**HIV**).
  - **Viral release** are *blocked by*; **Neuraminidase inhibitors** (**influenza**).

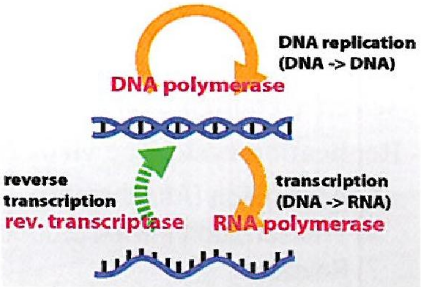
- **Retrovirus**; A **virus** that is *composed* of **RNA**, ***but*** have an **enzyme**, called **reverse transcriptase**, that ***gives them*** the **unique property** of ***transcribing*** *their* **RNA** ***into*** **DNA** *after entering* a **cell**. The ***new*** **DNA** is then ***incorporated*** into the ***host cell*** **chromosomal DNA** by an **integrase enzyme**, at which point the ***retroviral*** **DNA** is ***referred to*** as a **provirus**. **HIV** is a ***retrovirus*** [retro = backwards].


Cell
host DNA
host DNA
virus DNA
new virus proteins
copies of virus genes

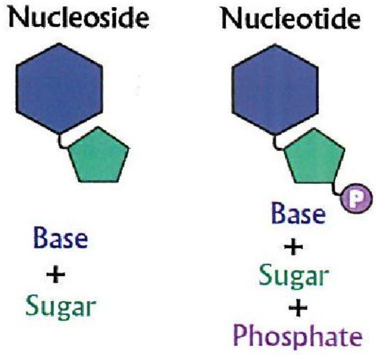
a virus enters a host cell

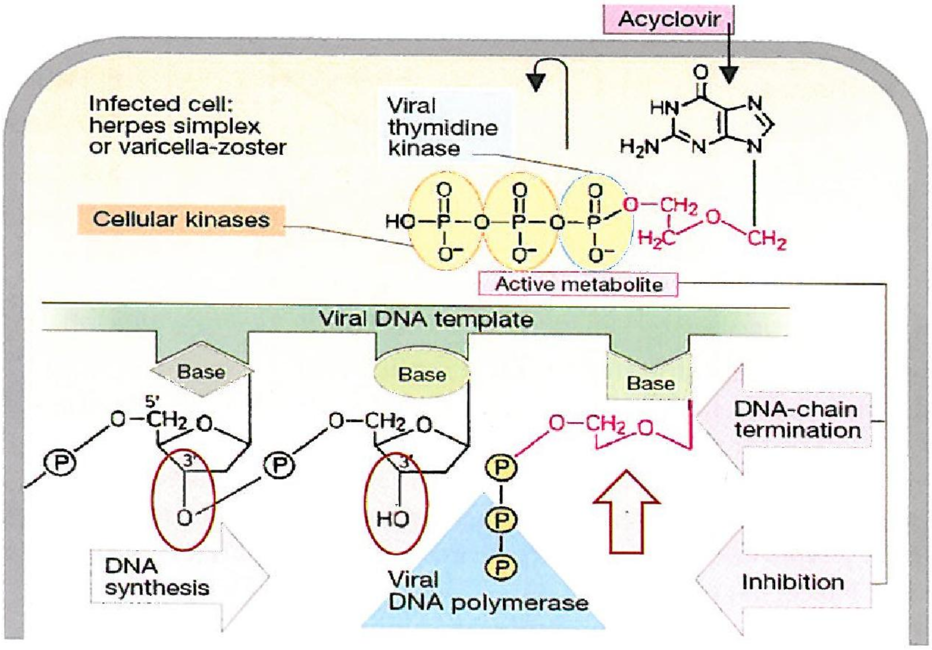
the virus inserts its DNA into the host's DNA

the cell makes virus genes and proteins as it reads its own DNA


DNA replication
(DNA -> DNA)
DNA polymerase
reverse
transcription
rev. transcriptase
transcription
(DNA -> RNA)
RNA polymerase

- **Reverse-transcriptase inhibitors** (**RTIs**) are a *class* of **antiretroviral drugs** used to ***treat*** **HIV infection** or **AIDS** and ***some cases*** **hepatitis B**.
- ***Without*** **reverse transcriptase**, the **viral** ***genome*** would *not* be **able** to ***incorporate*** into the **host cell**, *resulting in* ***failure to*** **replicate**.
- **RTIs** are ***more*** **selective** for **viruses** *because* **DNA production** by **reverse transcriptase** is ***very*** **different** from ***normal*** **human DNA** ***replication***.
- **RTIs** *come in* **3** ***forms***;
  - ***Nucleoside*** **Analog Reverse-Transcriptase *Inhibitors*** (**NARTIs** or **NRTIs**).
  - ***Nucleotide*** **Analog Reverse-Transcriptase *Inhibitors*** (**NtARTIs** or **NtRTIs**).
  - ***Non-nucleoside*** **Reverse-Transcriptase *Inhibitors*** (**NNRTIs**).
- **Nucleoside analogues** are ***nucleosides*** which ***contain*** a **nucleic acid *analogue*** and a **sugar**.
- **Nucleotide analogues** are ***nucleotides*** which ***contain*** a **nucleic acid *analogue***, a **sugar** and **one** to **three phosphate *groups***.
- **These agents** can be used ***against*** **hepatitis B virus**, **hepatitis C virus**, **herpes simplex**, and **HIV**.
- **Once** they are ***phosphorylated***, they work as **antimetabolites** by being ***similar enough*** to **nucleotides** to be ***incorporated*** into ***growing*** **DNA strands**; but they ***act as*** **chain terminators** (**3'-hydroxyl group** is *not present*) and ***stop*** **viral DNA polymerase**.


Nucleoside
Nucleotide
Base
+
Sugar
P
Base
+
Sugar
+
Phosphate


Acyclovir
Infected cell:
herpes simplex
or varicella-zoster
Viral
thymidine
kinase
Cellular kinases
Active metabolite
Viral DNA template
Base
Base
Base
5'
3'
3'
O
HO
P
P
DNA-chain
termination
DNA
synthesis
Viral
DNA polymerase
Inhibition

Antivirals for Herpesvirus Infections

- *Herpesviridae* is a **large family** of **DNA viruses**.
- The **members** of *this* **family** are also *known as* **herpesviruses**.
- The name is derived from Greek word **herpein** ("**to creep**"), *referring to* **latent**, ***recurring*** **infections**.
- There are more than **130 herpesviruses**, some of them from **mammals**, **birds**, **fish**, **reptiles**, **amphibians**, and **mollusks**.
- There are **9 herpesvirus** types known to ***infect*** **humans**, **Five** viruses are ***extremely*** widespread;

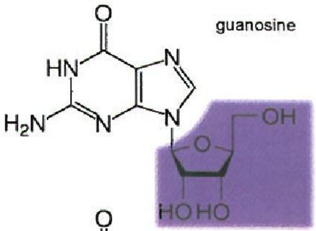
Name	Primary Target Cell	Pathophysiology	Site of Latency	Transmission
Herpes Simplex Virus-1 (HSV-1)	Mucoepithelial	Oral and/or genital herpes	Neuron	Close contact
Herpes Simplex Virus-2 (HSV-2)	Mucoepithelial	Oral and/or genital herpes	Neuron	Close contact
Varicella-Zoster Virus (VZV or **HHV-3)**	Mucoepithelial	Chickenpox and shingles	Neuron	Respiratory & close contact
Epstein-Barr Virus (EBV or **HHV-4)**	B cells & epithelial cells	Mononucleosis, several diseases and some cancers	B cell	Body fluids & close contact
Cytomegalovirus (CMV or **HHV-5)**	Monocyte, lymphocyte, and epithelial cells	Fever and inflammatory changes in multiple organs	Monocyte, lymphocyte	Body fluids; Saliva, urine, blood, tears, semen, breast milk

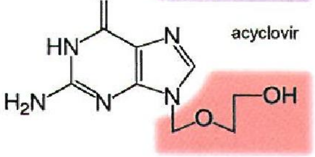
- **Antivirals** for **Herpesvirus infections** are ***effective*** **against** these **viruses** *exert their* **actions** ***during*** the **acute phase** of **viral infections** and are ***without*** **effect** *during* the **latent phase**.

Agents used to treat Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV)

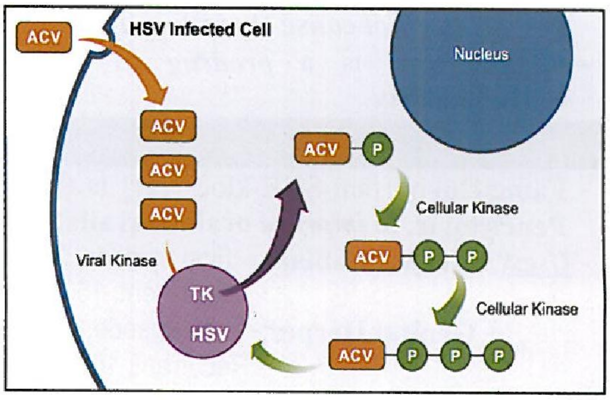
Acyclovir (Zovirax®)

- **Acyclovir** [ay-SYE-kloe-veer] (**Acycloguanosine**) is the ***prototypic*** **antiherpetic drugs**.
- ***Pharmacokinetics***;
  - ***Administration***; **IV**, **oral** or **topical** (systemic concentrations of topical preparations are undetectable).
  - ***Bioavailability***; *low* (15–30%) and is ***unaffected*** by **food**; **Valyl ester** of **Acyclovir** (**Valacyclovir**) has ***greater*** **oral bioavailability**.
  - ***Distribution***; **distributes *well*** throughout the **body**, *including* **CSF**.
  - ***Metabolism***; ***partially*** (small amounts) in the **liver**.
  - **Excretion**; **renally** and ***accumulates*** in *patients with* **renal failure**.
  - ***Half-life***: 4 hrs (Neonates) - 2-3 hrs (children 1-12 years) - 3 hrs (adults) - 20 hours (patients with anuria).





- ***Mechanism***; (**Antiherpes Drugs**)
  - *Activation*; **Acyclovir** (**ACV**) is a **Guanosine** *analog requires* **3 phosphorylation** *steps* for **activation**; **Virus-*infected*** cells are ***most*** **susceptible**;
    - * **Acyclovir** *is converted to* **Acyclovir Monophosphate** *by* **Thymidine Kinase (TK)** *enzyme*.
    - * **Acyclovir Monophosphate** is converted to the **di- & triphosphate** *by* **host cell kinases**.
  - **Acyclovir Triphosphate** ***competes*** with **Deoxyguanosine Triphosphate** as a ***substrate*** for **viral DNA polymerase** and is *itself* ***incorporated*** into the **viral DNA**, causing ***premature*** **DNA chain termination**.



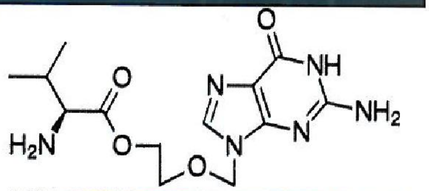
- ***Resistance***; - *Alteration* in **viral thymidine kinase** and/or **DNA polymerase** (*most commonly* in **immunocompromised patients**).
  - *Cross-resistant* to **Valacyclovir**, **Famciclovir** and **Ganciclovir**.
  - **Foscarnet**, **Cidofovir** and **Trifluridine** ***do not*** **require** ***activation by*** **viral thymidine kinase** and ***effective against*** **Acyclovir-*resistant*** **strains**.

- ***Uses***; - **Genital Herpes**; for 7-10 days (duration of therapy).
  - **Herpes Simplex Virus**; - **HSV Encephalitis**; 10 days; up to 14-21 days.
    - **Neonatal HSV Infection**; up to 14-21 days (*according to site of infection)*.
    - **HSV Mucocutaneous Infection (Herpes Labialis)**; for 5-10 days.
  - **Herpes Zoster (Shingles** and **Chickenpox)**; for 7-10 days.
- ***Dose***; - *Adult*: - **Oral; 200 mg 5 times daily - 400-800 mg 2-4 times daily**; *according to infection.*
    - **IV; 10 mg/kg IV** *every* **8 hours.**
  - *Child*: - **Oral; 200 mg Susp.** (10-20 mg/kg/dose) **4 times daily**; *according to infection.*
    - **IV; 10-20 mg/kg IV** *every* **8 hours.**

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; ***Depend on*** **the route of administration**;
  - *Topical*; **local irritation.**
  - *Oral*; **malaise, headache, diarrhea, nausea** and **vomiting.**
  - **IV**; **injection site reactions, nausea, vomiting** and ***reversible*** **renal dysfunction** or **neurologic effects** (may occur at high doses).
- ***Pregnancy***; **Recent study found *no* evidence of *increased* birth defects (Category; B).**

Valacyclovir (Valtrex®)



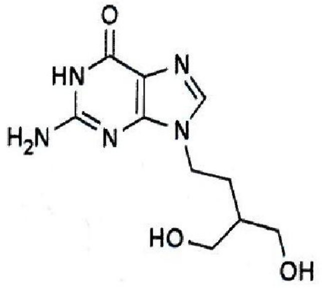
- **Valacyclovir** [val-a-SYE-kloe-veer] is the **L-valyl ester** of **Acyclovir**. It is ***rapidly*** *converted to* **Acyclovir** after **oral administration** by the **liver** (first pass enzymatic hydrolysis) and **intestine, serum levels** are **3** to **5 *times* greater *than* oral Acyclovir** and **oral bioavailability** is ~ **55%**.
- ***Uses***; - **Herpes Labialis (Cold Sores)**; 2 g orally every 12 hrs for 1 day.
  - **Genital Herpes**;- *First episode*; 1 g orally every 12 hrs for 10 days.
    - *Recurrent*; 500 mg orally every 12 hrs for 3 days.
  - **Herpes Zoster**; 1 g orally every 8 hours for 7 days.

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; ***same as*** **Acyclovir.**

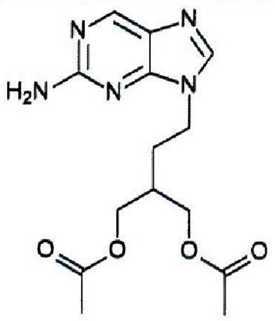
Herpes Labialis (Cold Sores)

Penciclovir (Denavir®)



- **Penciclovir** [pen-SYE-kloe-veer] is an ***acyclic* guanosine *derivative*.**
- *Because* **Penciclovir** is **absorbed** ***poorly*** when given **orally** it is used ***only*** as a ***topical*** **treatment** *for* **Herpes Simplex Labialis.**
- ***Mechanism***; ***As* Acyclovir**, *activation by* **phosphorylation** is catalyzed by the *virus-specified* **thymidine kinase** in ***infected*** **cells *inhibition*** of the **viral DNA polymerase** and ***block*** **DNA synthesis. *Unlike* Acyclovir, Penciclovir *not cause* chain termination.**
- **Famciclovir** is a ***prodrug*** of **Penciclovir** with ***improved*** **oral bioavailability.**

Famciclovir (Famvir®)

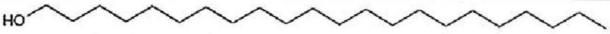


- **Famciclovir** [fam-SYE-kloe-veer] is the **di-acetyl ester *prodrug*** of **6-deoxy-Penciclovir**, to ***improve*** **oral bioavailability (77%).**
- ***Uses***; - **Herpes Labialis**;- First episode; 250 mg orally every 8 hrs for 7-10 day.
    - Recurrent; 1500 mg orally once; initiate therapy at first sign.
  - **Genital Herpes**;- First episode; 250 mg orally every 8 hrs for 7-10 day.
    - Recurrent; 1000 mg orally every 12 hrs; for 1 day.
  - **Herpes Zoster**; 500 mg orally every 8 hrs; for 7 day.

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; **headache, nausea** or **diarrhea** *may occur.*

Docosanol (Abreva®)



- **Docosanol** [doe-KOE-san-ole] (*known as* **behenyl alcohol**), is a ***saturated* 22-carbon *aliphatic* fatty alcohol** used traditionally as an **emollient**, **emulsifier** and **thickener** in **cosmetics**.
- **Docosanol** ***inhibits* fusion** *between* the **plasma membrane** and **HSV** ***envelope***, thereby ***preventing* viral entry** into **cells**.
- ***Topical*** **Docosanol cream** has been *approved by* **FDA** in 2000, for ***reducing*** the **duration** of **cold sores** or **fever blisters** *on the* **face** or **lips**.

Trifluridine (Viroptic®)

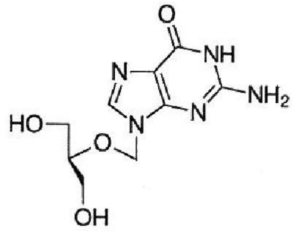
- **Trifluridine** [trye-FLURE-i-deen] (**Trifluorothymidine**) is a ***fluorinated*** **pyrimidine nucleoside** that ***inhibits*** **viral DNA** ***synthesis***.
- **Trifluridine eye *drops*** are used **kerato-conjunctivitis** and **keratitis** *due to* **HSV 1** and **2**.

- **Valomaciclovir (EPB-348)** is a ***next-generation*** **broad-spectrum antiviral** (not approved yet 10/2017) for the *treatment of* **Varicella-Zoster virus** and **Epstein-Barr virus** (**Mononucleosis**); ***once*-daily**.

Agents used to treat Cytomegalovirus (CMV)

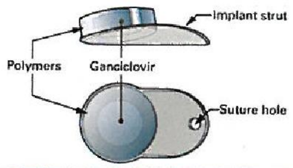
- **Cytomegalovirus** (**CMV**) [sy-toe-MEG-a-low-vy-rus] is a ***common*** **virus** that ***infects*** **people** of ***all*** **ages** and *can* cause ***serious*** **problems** in ***advanced*** **immunosuppression patients** (*organ transplant* or *HIV infection*) and **neonates *infected*** with the **virus *before*** they are **born** (**congenital CMV**).
- ***Dissemination*** of **infection** *results in* **end-organ disease**, *including* **retinitis, colitis, esophagitis, CNS disease** and **pneumonitis**.

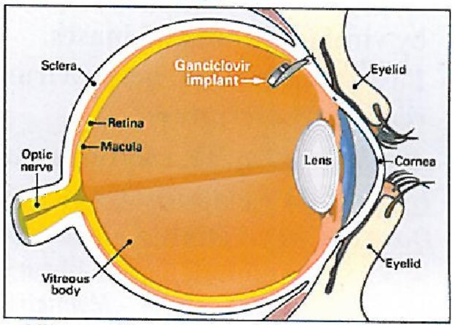
Ganciclovir (Cytovene®)



- **Ganciclovir** [gan-SYE-kloe-veer] is an ***acyclic*** **guanosine** ***analog*** (*analog of* **Acyclovir** that has **greater activity** ***against*** **CMV** *up to* **100 times** ***greater than*** that of **Acyclovir**). ***Like*** **Acyclovir**; **Ganciclovir** ***requires*** **activation** by **triphosphorylation** *before* ***inhibiting*** **viral DNA polymerase**.
- The ***first*** **phosphorylation step** is *catalyzed by* **virus-specified protein kinase phosphotransferase UL97** in **CMV-infected cells**.
- ***Bioavailability***; - **Fasting**: 5%. - *After* **food**: 6-9%. - *After* **fatty meal**: 28-31%
- **Valganciclovir** is the **L-valyl ester** of **Ganciclovir** to ***improve*** **oral bioavailability** of **Ganciclovir**.
- ***Distribution***: ***widely***, ***all*** **tissues** *including* **CSF & ocular tissue**.
- ***Formulations***; **Oral**, **IV** and ***intraocular*** **implant** (**Vitrasert®**).
- ***Uses***; - **CMV Retinitis**;
  - ***Initial***: 5 mg/kg IV at a constant rate over 1 hour, every 12 hours for 14 to 21 days.
  - ***Maintenance***: - **IV**; 5 mg/kg IV at a constant rate over 1 hour once a day, 7 days/week OR 6 mg/kg IV once a day, 5 days/week.
    - **Oral**: 1000 mg 3 times a day or 500 mg 6 times a day (every 3 hours while awake) with food.
  - **CMV *Prophylaxis***;
    - **HIV Patients**; 1000 mg orally 3 times a day with food.
    - **Transplant Patients**;
      - ***Initial***; 5 mg/kg IV over 1 hour every 12 hours for 7 to 14 days.
      - ***Maintenance***;
        - **IV**: 5 mg/kg IV once a day, 7 days/week or 6 mg/kg IV once a day, 5 days/week.
        - **Oral**: 1000 mg orally 3 times a day with food.
  - **CMV Colitis** or **Esophagitis** in **HIV Patients** (Off-label).

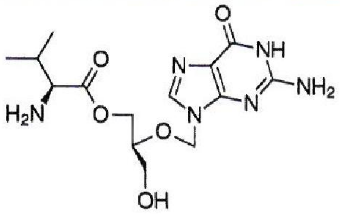
  "**Dose *must be* adjusted** in *patient with* **renal failure**"
- ***Side effects***; **Myelosuppression** (Neutropenia, Thrombocytopenia).
- **Ganciclovir** is **teratogenic** (**embryotoxic**).





- **Vitrasert®**; is an intraocular device consists of a 4.5 mg pellet of Ganciclovir coated by a laminated system of biocompatible polymers.
- This device was approved by the FDA in 1996 for treatment of Cytomegalovirus (CMV) retinitis in subjects with AIDS.
- The implant can be removed when depleted of drug, usually within five to eight months, and a new Vitrasert® Implant can be inserted.

Valganciclovir (Valcyte®)

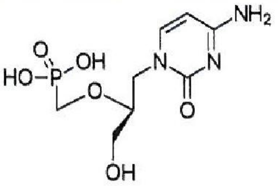


- **Valganciclovir** [val-gan-SYE-kloe-veer], is an **L-valyl ester** ***prodrug*** of **Ganciclovir**, It is ***rapidly*** *converted to* **Ganciclovir** after **oral administration.** ***Bioavailability***; *With* **food 60%** (***high*-fat meal *increases* AUC** by **30%**).
- ***Uses***; - **CMV Retinitis**; - ***Induction***: 900 mg orally twice a day for 21 days.
  - ***Maintenance***: 900 mg orally once a day.
  - **CMV *Prophylaxis***; 900 mg orally once a day.
  - **CMV Colitis** or **Esophagitis** in **HIV Patients** (Off-label).

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; **Vomiting, abdominal pain, diarrhea, headache, insomnia, peripheral neuropathy, retinal detachment** and **myelosuppression.**

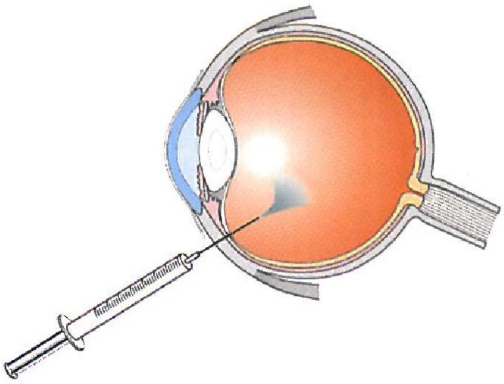
Cidofovir (Vistide®)



- **Cidofovir** [si-DOE-foe-veer] is a **cytosine *analog***, ***phosphorylation*** of **Cidofovir** to the ***active*** **diphosphate** is ***independent*** of **viral enzymes.**
- ***Administration***;
  - **IV** and **Intravitreal** (injection into vitreous humor between lens and retina).
    - **Intravitreal** of **Cidofovir** is ***associated with* risk** of **hypotony** and **uveitis.**
- ***Uses***; - **CMV Retinitis**; - ***Induction***; 5 mg/kg via IV infusion once a week for 2 consecutive weeks.
  - ***Maintenance***; 5 mg/kg via IV infusion once every 2 weeks.

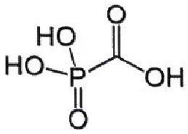
" ***Must*** administer **Probenecid *orally*** & **IV normal saline** with ***each* dose** of **Cidofovir** to ***reduce* risk** of **nephrotoxicity**"

  - **Smallpox Vaccine Reaction** (Off-label); 5 mg/kg via IV infusion once may be repeated 1 week later.
- ***Major side effects***; ***Dose-dependent*** **Nephrotoxicity** (***reduced*** with **pre-hydration** using **normal saline** and ***blocks*** **active tubular secretion** by ***high-dose*** of **Probenecid**), **proteinuria, azotemia, metabolic acidosis,** and **Fanconi's syndrome** *may occur.*



Intravitreal injection

Foscarnet (Foscavir®)



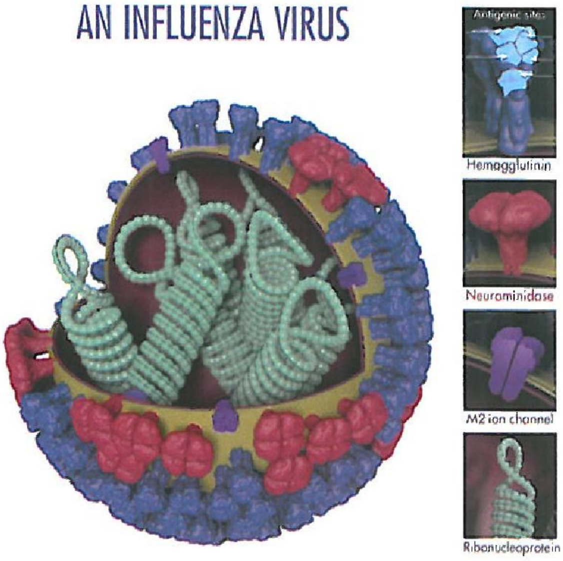
- **Foscarnet** [fos-KAR-net] is ***not*** a **purine** or **pyrimidine *analog***, it is a **Phosphonoformate** (a ***pyrophosphate derivative***) and ***does not*** **require *activation*** by **viral** (or **cellular**) **kinases**.
- **Foscarnet *inhibits*** **herpesvirus DNA polymerase, RNA polymerase** and **HIV *reverse* transcriptase.**
- ***Administration***; **IV** and **Intravitreal** (poorly absorbed orally and GI intolerance).
- ***Uses***; - **CMV retinitis, CMV gastroenteritis** and **acyclovir-*resistant* HSV infections.**
- ***Dose*** in **CMV retinitis**; - ***Induction***; 90 mg/kg IV (90- to 120-minute infusion) every 12 hours or 60 mg/kg IV (minimum 1-hour infusion) every 8 hours over 2 to 3 weeks depending on clinical response.
  - ***Maintenance***; 90 to 120 mg/kg IV (2-hour infusion) once a day.

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; **Nephrotoxicity, anemia, nausea fever, electrolyte *imbalance*** and **genital ulcer.**

Antivirals *for* Viral Respiratory Infections (VRIs)

- **Viral Respiratory Infections (VRIs)** ***commonly*** **affect** the ***upper*** or ***lower*** **respiratory tract.**
- **Viruses** that cause **VRIs** *include*; **respiratory syncytial viruses** (**RSV**), **influenza viruses**, **parainfluenza viruses**, **adenoviruses** and **rhinoviruses** (most common cause of common cold).
- **Influenza virus** ***strains*** are *classified by their*; **core proteins** (ie, **A**, **B** or **C**), **species** of **origin** (eg, **avian, swine**) and **geographic site** of ***isolation***.
- **Influenza A**, the ***only*** **strain** that causes **pandemics**, is ***classified into*** **16 H (hemagglutinin)** and **9 N (neuraminidase)**.
  - **H** = **Hemagglutinin**, a **protein** that *causes* **red blood cells** to **agglutinate**.
  - **N** = **Neuraminidase**, an **enzyme** that ***cleaves*** the **glycosidic bonds** of the **monosaccharide, neuraminic acid**.



  - *For example*; **H5N1** (**avian influenza "bird flu"**) virus designates an **influenza A** *subtype* that has a **type 5 hemagglutinin** (**H**) **protein** and a **type 1 neuraminidase** (**N**) **protein**.
  - **H1N1** = **Swine influenza**.
- **Influenza A** can ***infect*** a *variety of* **animal hosts**.
- **Influenza B** usually **infect** ***only*** **people**.
- **Immunization** ***yearly*** *against* **Influenza A** is the ***preferred*** **approach**.

Neuraminidase Inhibitors (NAIs)

- **Neuraminidase Inhibitors** (**NAIs**) are a *class* of **drugs** *which* ***block*** **viral neuraminidases** of the **influenza virus**, by ***preventing*** **reproduction** and ***release*** of ***new*** **virions** *from* **cell** to **cell**.

Oseltamivir (Tamiflu®)

Zanamivir (Relenza®)

- **Oseltamivir** [os-el-TAM-i-veer] and **Zanamivir** [za-NA-mi-veer] are ***effective*** **against** ***both*** **type A** and **type B influenza viruses**.
- ***Benefits***; - **Administration** ***before*** **exposure**; ***prevent*** **infection**.
  - ***Early*** **administration** *within* **24** to **48 hours** *after* the ***onset*** of **symptoms**; ***modestly*** *decrease* **intensity** and **duration** of **symptoms**.
- ***Pharmacokinetics***;
  - **Oseltamivir** is an ***orally*** **prodrug** that is ***rapidly*** **hydrolyzed** by the **liver** to its ***active*** **form**.
  - **Zanamivir** is ***not active*** **orally** and is **administered** ***via*** **inhalation**.
- ***Dose***; - **Oseltamivir**; ***Duration of therapy***: **5 days**;
  - <15 kg: 30 mg *orally* twice daily.
  - 15-23 kg: 45 mg *orally* twice daily.
  - 23-40 kg: 60 mg *orally* twice daily.
  - >40: 75 mg *orally* twice daily.
  - **Zanamivir**; **10 mg** (**2** ***inhalation tab.***) **twice** for **5 days**.
- ***Side effects***; - **Oseltamivir**; **GI discomfort** and **nausea** (can ***decreased*** by **taking** *with* **food**).
  - **Zanamivir**; **Headache, throat/tonsil pain** and **cough**.
- **Zanamivir** ***should be*** **used** *with* **caution** in **asthma** or **COP disease** (**bronchospasm** *may occur*).

Peramivir (Rapivab®)

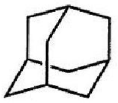
Laninamivir (Inavir®)

- **Peramivir** [per-AM-i-vir] and **Laninamivir** [LAN-e-NAM-i-veer] are a ***new agents*** in **NAIs**.
- **Peramivir** (Rapivab®) was ***approved*** for **IV administration** in 2014 for treatment of **Influenza**.
- **Laninamivir** was ***approved*** for **Influenza** in **Japan** (***treatment*** in 2010 and for ***prophylaxis*** in 2013) under the name **Inavir®** dry powder for **inhalation**.

- 23/2/2018; Japan's health ministry has approved **Baloxavir Marboxil** (Xofluza®) tablets, a drug that reportedly can kill influenza types A and B in as little as 1 day among some patients **(ONLY one tablet)**.

Adamantane Derivatives

- **Adamantane** is a ***cycloalkane*** (diamondoid), with a formula $C_{10}H_{16}$.
- **Amantadine (1-amino-adamantane)** and **Rimantadine (α-methyl Amantadine)** are ***Adamantane derivatives.***



Amantadine (PK-Merz®) (Symmetrel®)	**Rimantadine** (Rymanta®)

- **Amantadine** [a-MAN-ta-deen] and **Rimantadine** [ri-MAN-ta-deen] are **active *against* Influenza A *only*.**⬅ , due to ***widespread* resistance**, they are *usually* ***not*** **recommended.**
- **Amantadine** is an ***antiparkinsonian drug.***
- ***Mechanism***; **Amantadine** and **Rimantadine** ***interfere*** with the **function** of the **viral M2 protein**, *possibly* ***blocking*** **uncoating** of the **virus** ***particle*** and ***preventing*** **viral release.**
- ***Dose***; **Influenza A**; **Amantadine**; 100 mg twice daily or 200 mg once. **Rimantadine**; 100 mg twice daily.
- ***Side effects***; - **GI intolerance.**
  - **Amantadine; CNS side effects; insomnia, dizziness** and **ataxia.**
- **Tromantadine** (Viru-Merz®) is ***another Adamantane derivative*** *available as* **topical gel** for **HSV.**

Ribavirin

Ribavirin

- **Ribavirin** [rye-ba-VYE-rin] is a ***synthetic* guanosine analog**, is *effective* ***against*** a **broad spectrum** of **RNA** and **DNA viruses**; - **Respiratory Syncytial Virus (RSV)** ***infection.***
  - **Hepatitis C** (in combination with other antiviral drugs).
  - **Viral Haemorrhagic Fever.**
- ***Mechanism***; **Ribavirin** is ***phosphorylated*** **intracellularly** by **host cell enzymes. Ribavirin triphosphate** *appears* to ***interfere*** with the ***synthesis*** of **guanosine triphosphate**, ***inhibits*** the **replication** of a ***wide range*** of **DNA** and **RNA viruses.**
- ***Administration***; - ***Inhalation***; for **RSV infection.**
  - ***Oral***; **bioavailability** 64%, ***increased with*** **fatty meal.**
- ***Dose***; for **Hepatitis C** (Genotype 1, 4); - **<75 kg**: 1000 mg/day orally divided every 12 hours.
  - **≥75 kg**: 1200 mg/day orally divided every 12 hours.
- ***Side effects***; - ***Dose-dependent*** *transient* **anemia**; **monitoring** is ***essential.***
  - **Nausea, fatigue, headache, myalgia, arthralgia** and **insomnia.**

- **Pregnancy category X.**
- ***Effective*** **birth control** method ***must be*** **taken** to ***avoid*** **pregnancy** *during* **therapy** & for **6 months *after*** **completion** of **treatment** in **both female *patients*** & in **female partners** of **male *patients*** who are ***taking*** **Ribavirin therapy.**

FDA Warning

* ***Should not*** be **used alone** for **chronic hepatitis C** (*not effective*).

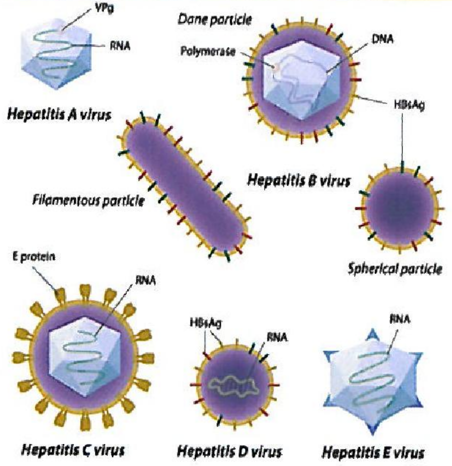
* **Hemolytic anemia**; ***Should not*** be **used** in ***unstable*** **cardiac disease** (**monitoring** is ***essential***).

* **Teratogenic (Category X)**; ***Avoid*** in **women** *who are* **pregnant** and in **male partners** of **women** *who are* **pregnant *during*** and ***after*** **6 months** of **therapy.**

Seasonal Flu Vaccine (Flu Shots)

- The **World Health Organization (WHO)** and the **Centers** for **Disease Control** and **Prevention (CDC)** ***recommend*** **yearly *vaccination*** for *nearly* ***all*** **people** over the age of **6 months**, especially those at high risk.
- **Flu vaccines** cause **antibodies** to ***develop*** in the body *about* **2 weeks *after*** **vaccination**, to ***protect*** the **body *against*** **infection** with the **viruses** that are in the vaccine.
- ***Each year***, **3 strains** are ***chosen*** for **selection** in that **year's flu vaccination** by the **WHO**.
- The ***chosen*** **strains** are the **H1N1**, **H3N2**, and **Type-B strains** thought ***most likely*** to cause ***significant*** **human suffering** in the **coming season**.
- The **vaccines** are ***generally*** **safe** (**Fever** may occurs in **children** vaccinated; 5-10%).
- **Vaccines** are **manufactured *using*** **virus** *grown in* **eggs**; It ***should not*** be **given** to those with ***severe*** **allergies** to **eggs** or to ***previous*** **versions** of the **vaccine**.
- ***Dose***; - **6-35 months (3 years)**; **0.25 mL *once*** **yearly** (***second*** **injection** 0.25 mL with **1 month** *interval* ***only*** in **first time** of **vaccination**).
  - **3-8 years**; **0.5 mL *once*** **yearly** (***second*** **injection** 0.5 mL with **1 month** *interval* ***only*** in **first time** of **vaccination**).
  - **≥ 9 years**; **0.5 mL *once*** **yearly.**

Antivirals *for* Hepatitis Viruses



- **Viral hepatitis** is **liver** ***inflammation*** *due to* a **viral infection**, it may present in **acute** (recent infection, relatively rapid onset) or **chronic**.
- The ***most common*** causes of **viral hepatitis** are **five viruses**; **Hepatitis A**, **B**, **C**, **D** and **E**.
- **Hepatitis B** (**DNA virus**) and **Hepatitis C** (**RNA virus**) are the ***most common*** causes of **chronic hepatitis**, **cirrhosis** and **hepatocellular carcinoma** and are the ***only*** **hepatic viral infections** for which **therapy** is ***currently*** **available**.
- ***Other*** **viruses** that can also cause **hepatitis** *include* **cytomegalovirus**, **Epstein–Barr virus** & **yellow fever**.
- **Hepatitis A** & **B** can be ***prevented by*** **vaccination**.
- The **vaccine** for **Hepatitis B** ***protects*** *against* **Hepatitis D**.
- **Vaccination** is ***recommended*** by the WHO in the ***first*** **day** of life (*if possible*).
- **Hepatitis A** & **E infection** is ***commonly*** caused by **oral ingestion** of ***contaminated*** **food** or **water**, but it is ***not*** a **chronic disease**.
- **Hepatitis B**, **C** & **D infection** *usually* **occur** as a *result of* ***parenteral*** **contact** with ***infected*** **body fluids**.
- In **2013** *about* **1.5 million people died** *from* **viral hepatitis** (new study: 2016)

Antivirals *for* Hepatitis B Virus (HBV)

- *As of* **2010**; **7 drugs** were ***approved for*** treatment of **chronic HBV** ***infection***;
  - **2** ***injectable***; **Interferons** (**PEG-interferon alfa-2a** and **Interferon alfa-2b**).
  - **5** ***oral***; **Nucleoside/Nucleotide** ***Analogues*** (**Lamivudine**, **Adefovir**, **Tenofovir**, **Entecavir** & **Telbivudine**).

Interferon alpha (IFN-α)

- **Interferons** [in-ter-FEER-on] are a *family of* ***naturally occurring*** **cytokines** (***signaling*** **proteins**), that ***exert*** **complex antiviral**, **immunomodulatory** and **antiproliferative** ***actions***.
- **Interferons** were ***first described*** in **1957** (**named** *for* its ***ability to*** **interfere** with **viral** ***proliferation***).
- 3 ***forms*** of **Interferon**;
  - **Alpha** (α); **Chronic hepatitis B** & **C**, **Genital warts**, ***some types*** of **Leukemia** and **Kaposi sarcoma**.
  - **Beta** (β); **Multiple sclerosis**.
  - **Gamma** (γ); **Chronic Granulomatous Disease**.
- The ***selective*** **antiviral action** of **IFN-α** is ***primarily*** due to ***activation*** of a **host cell ribonuclease** that *preferentially* ***degrades*** **viral mRNA**.
- **IFN-α** *also*;
  - * ***Induction*** of **intracellular signals** *after* ***binding to*** *specific* **cell membrane receptors**, *resulting* in ***inhibition*** of **viral** ***penetration***, ***translation***, ***transcription***, **protein** ***processing***, ***maturation*** and ***release***
  - * **Immunomodulatory** ***effect*** that ***enhances*** **phagocytic** ***activity*** of **macrophages** and **cytotoxic activity** of **T-lymphocytes**.
- **Polyethylene glycol** (**PEG**) is *linked to* **Interferon** to ***make it*** (**PEG-interferon**) ***last*** **longer** in the **body**; ***larger*** **molecular size**; ***delays*** **absorption**, ***increase*** **duration of action** & ***decreases*** **clearance**.
- **Interferon** is ***not active*** **orally** and ***administered*** **IM**, **SC**, or **IV**.
- **PegIFN-α-2a** *has* ***similar*** or ***slightly*** **better efficacy** with ***improved*** **tolerability** than **PegIFN-α-2b**.
- ***Dose***;
  - **PegIFN-α-2a** *for* **Hepatitis C** (**NOT USED ALONE**) & **Hepatitis B**; **180 mcg SC once** ***weekly***.
  - **PegIFN-α-2b** *for* **Hepatitis C** (**NOT USED ALONE**); **1.5 mcg/kg SC once** ***weekly***.
  - **IFN-α-2b** *for* **Hepatitis C** (**NOT USED ALONE**); **3 million IU IM** or **SC 3 times** a ***week***. and **Hepatitis B**; **30-35 million IU** ***per week*** **IM** or **SC**, either as;
    - **5 million IU once** a **day** OR as **10 million IU 3** ***times*** a ***week***.

"**PegIFN-α** ***may*** use as **monotherapy** *in* **Chronic Hepatitis C** (**CHC**) **patients** ***if*** **contraindications** or ***significant*** **intolerance** to **antiviral drugs**"

- ***Side effects***;
  - **Flu-like symptoms** (**fever**, **chills**, **myalgias**, **arthralgias** and **GI disturbances**); typically **occurs** *within* **6 hours** ***after*** **dosing**, occur in ***more than*** **30%** of patients during the **first week** of **therapy** and ***tends to*** **resolve** *upon* ***continued*** **administration**.
  - **Fatigue**, **mental depression** and **weight loss**.

Lamivudine (Zeffix®) (Epivir®)

- **Lamivudine** [la-MIV-yoo-deen] is a ***cytidine analog*** is an ***inhibitor*** of ***both*** **Hepatitis B Virus (HBV)** and **Human Immunodeficiency Virus (HIV)**.
- **Lamivudine** is ***phosphorylated*** by **host cellular *enzymes*** to the **triphosphate (*active*) form.**
- ***Mechanism***; **Lamivudine** is a **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** *works by* ***blocking*** the **HIV *reverse transcriptase*** and **Hepatitis B virus *polymerase*.**
- ***Resistance*** to **Lamivudine** *may* **occur** and has been *associated with* ***flares*** of **hepatitis** & ***progressive*** **liver disease** (***exacerbation*** of **hepatitis B**); **Lamivudine** cause ***rapid*** and ***potent*** **virus suppression**, **chronic therapy** may cause **emergence *of* resistance** (occur in 15–30% of patients at 1 year and 70% at 5 years of therapy). ***Cross-resistance*** *between* **Lamivudine** and **Emtricitabine** or **Entecavir** *may occur.*
- ***Dose***; - **HIV Infection; 150 mg orally *twice*** a **day** OR **300 mg orally *once*** a **day**.
  - **Chronic Hepatitis B; 100 mg orally *once*** a **day**. "**Dose *must* be adjusted** in *patient with* **renal failure**"
- ***Side effects***; ***Excellent*** **safety profile** (Headache, nausea and dizziness are rare).
- ***Precautions***; **Lactic acidosis, hepatomegaly** and ***severe acute*** **Exacerbation** of **hepatitis B** *may result.*

Adefovir Dipivoxil (Hepsera®)

- **Adefovir Dipivoxil** [ah-DEF-o-veer die-pih-VOCKS-ill] is a ***prodrug*** of **Adefovir**.
- **Adefovir** is an ***acyclic*** **adenine nucleotide *analog*** that is ***phosphorylated*** by **cellular kinases** to **Adefovir Diphosphate**, which is then ***incorporated into*** **viral DNA**.
- **Adefovir** is a **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**.
- ***Resistance***; ***Unlike*** **Lamivudine**; **Adefovir** cause ***slow*** **virus suppression**, **emergence *of* resistance** is **rare *during*** the **first year** of **therapy**, it *approaches* **30%** at the ***end*** of **4 years**.
- ***Dose***; **Chronic Hepatitis B; 10 mg orally *once*** a **day**. "**Dose *must* be adjusted** in *patient with* **renal failure**"
- ***Side effects***; **hematuria, asthenia (weakness)** and ***dose-dependent*** **nephrotoxicity**.
- ***Precautions***; ***Exacerbation*** of **hepatitis B** and **nephrotoxicity** *may result.*

Entecavir (Baraclude®)

- **Entecavir** [en-TECK-ah-veer] is a ***guanosine analog*** for the ***treatment*** of **HBV infections**.
- Following *intracellular* ***phosphorylation*** to the **Entecavir Triphosphate**, it ***competes*** with the natural *substrate*, **Deoxyguanosine Triphosphate**, for ***viral*** **reverse transcriptase (NRTIs)**.
- **Entecavir** is *effective* ***against*** **Lamivudine *-resistant*** **strains** of **HBV**.
- **Entecavir** appears to have a ***higher*** **barrier** to the **emergence *of* resistance** *than* **Lamivudine**.
- ***Oral bioavailability*** *approaches* **100%** *but* is ***decreased by*** **food** (**Entecavir** *should be* **taken** on an ***empty*** **stomach**). "**Dose *must* be adjusted** in *patient with* **renal failure**"
- ***Dose***; - ***Nucleoside-inhibitor-therapy-naive*** (≥16 years): **0.5 mg orally *once*** a **day**.
  - **Lamivudine-*refractory*** (≥16 years): **1 mg orally *once*** a **day**.
  - ***Decompensated*** **liver disease** (≥16 years): **1 mg orally *once*** a **day**.
- ***Side effects***; ***well*** **tolerated** (headache, fatigue, dizziness and nausea *may occur*).
- ***Precautions***; **Lactic acidosis, hepatomegaly** and ***severe acute*** **Exacerbation** of **hepatitis B** *may result.*

Telbivudine (Tyzeka®) (Sebivo®)

- **Telbivudine** [tel-BIV-yoo-dine] is a ***thymidine analog*** for the ***treatment*** of **HBV infections**.
- Following *intracellular* ***phosphorylation*** to the **Telbivudine Triphosphate**, it ***competes*** with the natural *substrate*, **Thymidine Triphosphate**, *resulting* in ***incorporation into*** **viral DNA** and **chain *termination***. **Emergence *of* resistance** *may occur.*
- ***Dose***; **600 mg orally *once*** a **day** (with or without food)."**Dose *must* be adjusted** in *patient with* **renal failure**"
- ***Side effects***; **Fatigue, *increased* creatine kinase** *levels*, **headache, abdominal pain, *upper* respiratory infection (cough), nausea** and **vomiting**.
- ***Precautions***; **Lactic acidosis** and ***severe acute*** **Exacerbation** of **hepatitis B** *may result.*

Tenofovir Disoproxil Fumarate (TDF) (Viread®)

- **Tenofovir** [te-NOE-fo-veer] is a ***nucleotide analog*** of **adenosine** in use as an ***antiretroviral agent*** (used for **HIV**), has ***recently gained*** **licensure** for the ***treatment*** of **patients** *with* **chronic HBV infection**.
- ***Dose***; **300 mg orally *once*** a **day**. "**Dose *must* be adjusted** in *patient with* **renal failure**"
- ***Side effects***; **Fatigue, diarrhea, nausea** and **pain**.
- ***Precautions***; **Lactic acidosis** and ***severe acute*** **Exacerbation** of **hepatitis B** *may result.*
- In **2016 Vemlidy®** (**Tenofovir Alafenamide**), was ***approved***.

Hepatitis A/B Vaccine

Hepatitis A Vaccine

- **Hepatitis A vaccine** in ***most countries*** is an ***inactivated*** (*killed*) **vaccine**; **2 doses** for ***at least*** **6 months** ***apart***.
- **Live attenuated hepatitis A vaccines** are ***manufactured*** and ***used*** **mainly** in **China** and ***sporadically*** in the *private sector* in **India**; **1 dose**.
- ***Dose***; **Havrix®**; (booster dose "second dose" administered anytime between 6 and 12 months later);
  - **≥ 1 year and adolescents; 2 doses IM (0.5 mL); 0-, 6** to **12-month**.
  - **Adult; 2 doses IM (1 mL); 0-, 6** to **12-month**.

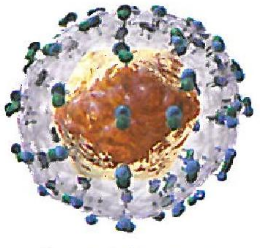
Hepatitis B Vaccine

- **Hepatitis B vaccine** is an ***inactivated*** (*killed*) **vaccine**, *made from* **parts** of the **hepatitis B virus**.
- The ***complete*** **vaccination** ***series*** *consists of* **3 doses** of **vaccine**; the ***first*** **2 doses** are *usually* ***given*** **1 month** ***apart***, with the **3rd dose 1–12 months** ***later***.
- ***Dose***; **Engerix-B®**; **< 19 years; 3 doses IM** (**0.5 mL** or **10 mcg** ***each***); **0-, 1-, 6-month**.
  > 20 years; 3 doses IM (**1 mL** or **20 mcg** ***each***); **0-, 1-, 6-month**.
- **Hepatitis B vaccine schedules for newborn infants** (R; Advisory Committee on Immunization Practices; ACIP);
  - A) **Single antigen** + **Combination vaccine** (**2017 Vaccination Schedule in Egypt**);
    - **4 doses** of **vaccine**; **0-(*within* 12 hours), 2-, 4-, 6-month**.
    - **Infants born to HBsAg-*positive* mothers: 0.5 mL IM *within* 12 hours of birth PLUS hepatitis B immune globulin (HBIG)**, *followed by*; **3 additional hepatitis B vaccine doses; 2-, 4-, 6-month**.
  - B) **Single-antigen vaccine**;
    - **3 doses** of **vaccine**; **0-(*within* 12 hours), 1-2, 6-18 month**.
    - **Infants born to HBsAg-*positive* mothers: 0.5 mL IM *within* 12 hours of birth PLUS hepatitis B immune globulin (HBIG)**, *followed by*; **2 additional hepatitis B vaccine doses; 1-2, 6-month**.

Hepatitis A+B Vaccine

- ***Dose***; - **Twinrix®**; > 18 years (approved only); **3 doses IM (1 mL); 0-, 1-, 6-month**.
  - **Twinrix® Paediatric** (1 year up to and including 15 years); **3 doses IM** (1 mL); **0-, 1-, 6-month**.

Antivirals *for* Hepatitis C Virus (HCV)



Hepatis C Virus (HCV)

- **Hepatitis C** is an ***infectious disease*** caused by the **hepatitis C virus (HCV)** that *primarily* **affects** the **liver**, **HCV** is a ***small***, ***enveloped***, ***single-stranded***, ***positive-sense*** **RNA virus**.
- ***During*** the **initial infection** people ***often*** have ***mild*** or ***no*** **symptoms**.
- ***Early*** on **chronic infection** typically has ***no*** **symptoms**.
- *Over* ***many*** **years** however, it often ***leads*** to **liver disease** and **cirrhosis**.
- In ***some cases***, those with **cirrhosis** will ***develop*** **complications** such as **liver failure**, **liver cancer**, or ***dilated*** **blood vessels** in the **esophagus** (**esophageal varices**) and **stomach** (**gastric varices**).
- **HCV** is ***spread*** *primarily* by **blood-to-blood** ***contact***.
- ***Globally***, an *estimated* **71 million** ***people*** have **chronic hepatitis C** ***infection*** [WHO Global hepatitis report, 2017]
- *Approximately* **399,000** ***people*** **die** *each* **year** from **hepatitis C**, *mostly from* **cirrhosis** and **hepatocellular carcinoma**.
- **Chronic infection** can be ***cured*** about **95%** of the **time** with **antiviral medications** such as **Sofosbuvir**, **Simeprevir** or ***other*** **new antiviral medications** and **regimens**.
- **Peginterferon** and **Ribavirin** were ***earlier*** **generation treatments** which had a **cure rate** of ***less than*** **50%** and ***greater*** **side effects**.
- There is **currently** ***no*** **vaccine** for **hepatitis C**; however research in this area is ongoing.
- There have been **7 genotypes** of are **HCV** ***discovered***:
  - * **Genotype 1**; most common genotype worldwide (46.2% of the population of the world is infected with hepatitis C).
  - * **Genotype 2**; about 9.1% of the cases of hepatitis C worldwide, always has been one of the easiest genotypes to treat.
  - * **Genotype 3**; is the second most prevalent genotype worldwide (about 30% of the population worldwide), genotype 3 is the most difficult to treat.
  - * **Genotype 4**; mostly confined to Africa (about 90% of the genotypes in Egypt), Many of the same medications to treat genotype 1 can be used to treat genotype 4.
  - * **Genotype 5**: has almost exclusively been found in South Africa.
  - * **Genotype 6**: about 5.4% of the worldwide population of hepatitis C and is mostly found in Southeast Asia.
  - * **Genotype 7**: There has only been a small number of people. They have all been from the Congo.

Interferon alpha-2b (IFN-α-2b) + Ribavirin

- In **1998 FDA** *approves* **Rebetron®**; **combination therapy** *containing*; **Rebetol®** (**Ribavirin**) capsules and **Intron® A** (**Interferon alfa-2b**, recombinant) injection for the *treatment* of **HCV**;
- *Dose*;
  - **Intron® A** (**Interferon alfa-2b**); **3 million units SC 3** ***times*** **weekly**, **PLUS**
  - **Rebetol®** (**Ribavirin**); - **<75 kg**; 1000 mg/day. - **≥75 kg**; 1200 mg/day.
- *Duration of therapy*; - **Genotype 1**; **48 weeks**. - **Genotype 2** and **3**; **24 weeks**.
- *Response rates*; - **Genotype 1**; **29%**. - **Genotypes 2** and **3**; **62%**.

PEG-Interferon alpha-2b (PegIFN-α-2b) + Ribavirin

- **PEG-Intron®** (**PegIFN-α-2b**) **PLUS** **Rebetol®** (**Ribavirin**) was also *approved* in **2001** to treat **HCV**.
- *Dose*;
  - **PEG-Intron®** (**PegIFN-α-2b**); **1.5 mcg/kg SC once** ***weekly***, **PLUS**
  - **Rebetol®** (**Ribavirin**); - **<75 kg**; 1000 mg/day. - **≥75 kg**; 1200 mg/day.
- *Response rates*; - **Genotype 1**; **41%**. - **Genotypes 2** through **6**; **75%**.

PEG-Interferon alpha-2a (PegIFN-α-2a) + Ribavirin

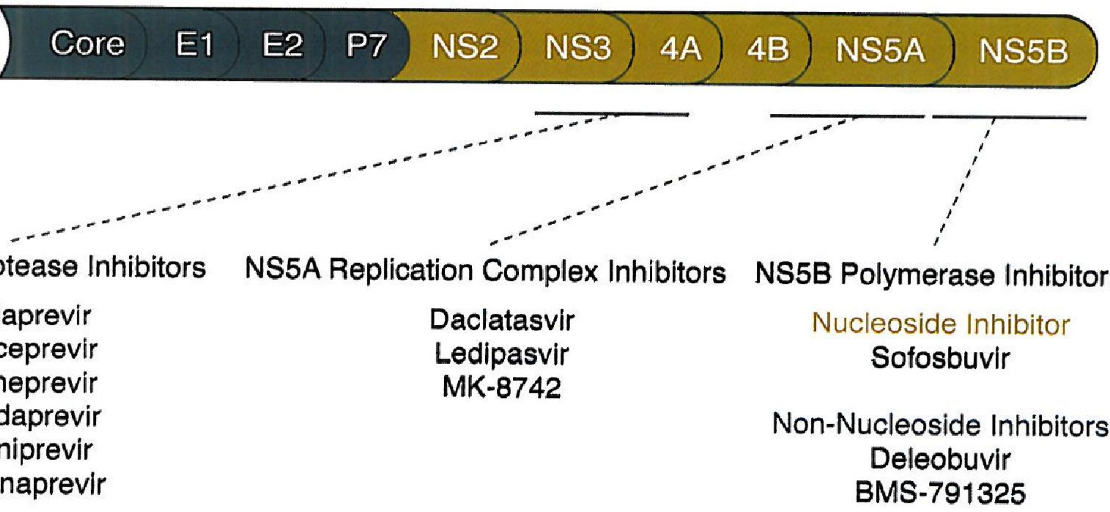
- **Pegasys®** (**PegIFN-α-2a**) was *approved* to treat **HCV** in **2002**.
- *Dose*; - **Pegasys®** (**PegIFN-α-2a**); **180 mcg SC once** ***weekly***, **PLUS**
  - **Copegus®** (**Ribavirin**); - **<75 kg**; 1000 mg/day. - **≥75 kg**; 1200 mg/day.
- *Response rates*; - **Genotype 1**; **44-51%**. - **Genotypes 2** and **3**; **82%**.

Interferon alpha-2b (IFN-α-2b) + Ribavirin Oral Solution

- In **2003** **Intron® A** (**Interferon alfa-2b**) **PLUS** **Rebetol®** **oral solution** (**Ribavirin**) *approved for* treating **pediatric** *patients* with *chronic* **HCV**.

Boceprevir (Victrelis®) OR Telaprevir (Incivek®)

- In May **2011** **FDA** was *approved* **Boceprevir** [boe-SE-pre-vir] and **Telaprevir** [tel-A-pre-vir] for used **one** of *them* in **combination** ***with*** **PEG-Interferon** **PLUS** **Ribavirin** for the *treatment* of *chronic* **HCV** in people with **Genotype 1**.
- **Boceprevir** and **Telaprevir** are **NS3/4A Protease Inhibitor** (**1st generation protease inhibitors**); **binds** *reversibly* **to nonstructural protein 3** (**NS 3**) *serine* **protease** and *inhibits* **replication** of the **hepatitis C virus**.
- **Viral protease** is the **viral enzyme** *responsible for* **cleavage** of the **viral polyprotein** into a *number of essential* **enzymes** and *several* **structural proteins**.
- The *inhibition* **prevents** *maturation* of the **viral particles** and *results* in the *production* of *noninfectious* **virions**.


Core
E1
E2
P7
NS2
NS3
4A
4B
NS5A
NS5B
NS3/4A Protease Inhibitors
Telaprevir
Boceprevir
Simeprevir
Faldaprevir
Vaniprevir
Asunaprevir
NS5A Replication Complex Inhibitors
Daclatasvir
Ledipasvir
MK-8742
NS5B Polymerase Inhibitors
Nucleoside Inhibitor
Sofosbuvir
Non-Nucleoside Inhibitors
Deleobuvir
BMS-791325

HCV-coding proteins and their representative direct-acting antiviral agents (DAAs)
Structural proteins are; core, E1, E2 and p7
Non-structural (NS) proteins are; NS2, NS3, NS4A (4A), NS4B (4B), NS5A and NS5B

- *Drug Interactions*; *All* **Protease Inhibitors** (**PIs**) are *substrates* for the **CYP3A4** *isoenzyme* and by other **CYP450** *isoenzymes*.

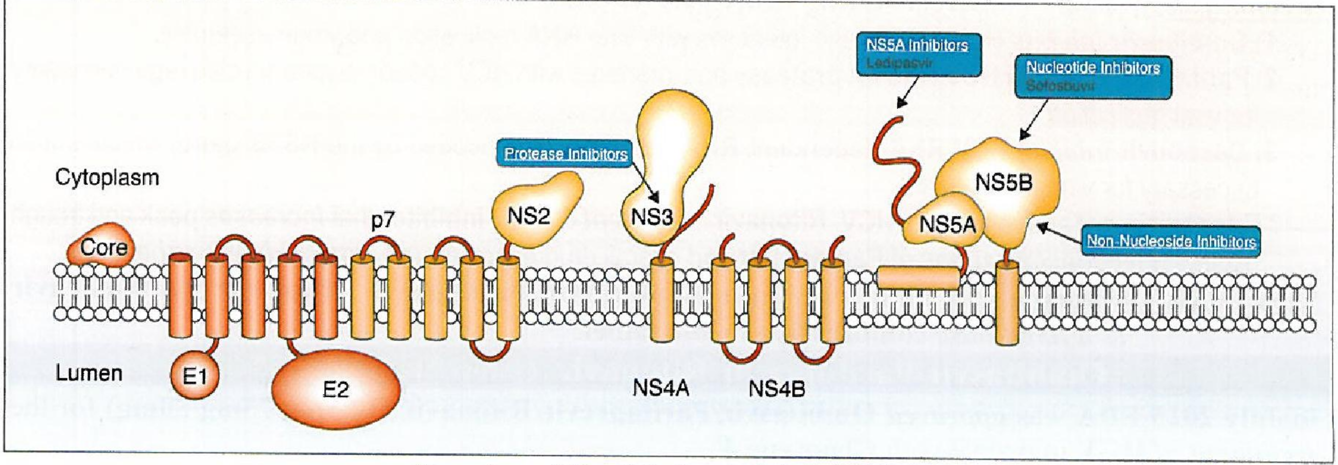
- **Protease inhibitors** were the ***first class*** of **Direct-Acting Antivirals (DAAs)**.
- ***Dose***;
  - **Boceprevir**; **800 mg orally** ***every*** **8 hrs** *with* **food** **OR** **Telaprevir 1,125 mg orally twice daily** *with* **food** **PLUS** - **PegIFN-α-2a**; **180 mcg SC once** ***weekly***, **PLUS**
    - **Ribavirin**; - **<75 kg**; 1000 mg/day. - **≥75 kg**; 1200 mg/day.
- ***Duration of therapy***; **28, 36** or **48 weeks.**
- ***Response rates***; - **Triple combination therapy** with **Boceprevir** are ***up to*** **66%** in **HCV genotype 1.**
  - **Triple combination therapy** with **Telaprevir** are ***up to*** **79%** in **HCV genotype 1.**
- On August 12, 2014, Vertex Pharmaceuticals announced that it would discontinue production of its brand of Telaprevir, Incivek and in January 2015, Merck announced that they would be voluntarily withdrawing Victrelis from the market; due to falling demand for the drug caused by competition from newer hepatitis C treatments.

Simeprevir (Olysio®)

- In **May 2013 FDA** was ***approved*** **Simeprevir** [sim-E-pre-vir] (**150 mg orally** **once** ***daily*** *with* **food**) for used in **combination** ***with*** **PEG-Interferon PLUS Ribavirin** for the ***treatment*** of ***chronic*** **HCV** in people with **Genotype 1**.
- **Simeprevir** is ***off-label*** used for **Genotype 4**.
- **Simeprevir** is a **NS3/4A protease inhibitor** (**2nd generation**) was as ***developed by*** **Medivir AB** and **Janssen Pharmaceutica.**
- ***Response rates***; ***up to*** **80%** and ***most people*** were treated for **24 weeks.**
- ***Drug Interactions***; **Like** ***other*** **PIs**; is ***substrates*** for the **CYP3A4** *isoenzyme.*

Sofosbuvir (Sovaldi®)

- In **December 2013 FDA** was ***approved*** **Sofosbuvir** [soe-FOS-bue-vir] (**400 mg orally** **once** ***daily*** *with* or *without* **food**) for used in **combination** ***with*** **Ribavirin** ***alone*** **OR** **Ribavirin PLUS PEG-Interferon-alfa** for the ***treatment*** of ***chronic*** **HCV** in people with **Genotype 1, 2, 3** or **4.**
- **Sofosbuvir** is ***prodrug*** and ***categorized as*** a **Direct-Acting Antiviral (DAA).**
- ***Mechanism***; **Sofosbuvir** is in the ***nucleotide analog*** works by ***blocking*** the **HCV NS5B RNA-dependent RNA** ***polymerase***, also ***essential for*** **viral replication**, and *acts as* a **chain terminator.**
- In the HCV lifecycle, replication requires NS5B both to copy the RNA genome and to transcribe messenger RNA. These essential steps in the lifecycle of HCV are critical for viral replication, and thus inhibition of NS5B prevents viral propagation.



Overview of Direct-Acting Antivirals (DAAs)

- ***Duration of therapy***; **12 weeks (Genotype 1, 2, 4)** or **24 weeks (Genotype 3).**
- ***Response rates***; - **Genotype 1**; **90%.** - **Genotypes 4**; **96%.**
- **Sofosbuvir NOW** is used in **combination** ***with*** **Simeprevir**, **Ledipasvir**, **Daclatasvir** or **Velpatasvir** ***with*** or ***without*** **Ribavirin** {**Interferon-FREE therapy**}.
- Sofosbuvir was discovered in 2007 by Michael Sofia, a scientist at Pharmasset, and the drug was first tested in people in 2010. In 2011 Gilead Sciences bought Pharmasset for about $11 billion.
- ***Drug Interactions***; **Like** ***other*** **PIs**; is ***substrates*** for the **CYP3A4** *isoenzyme.*
- ***Most Common side effects***; **Fatigue** and **headache**.

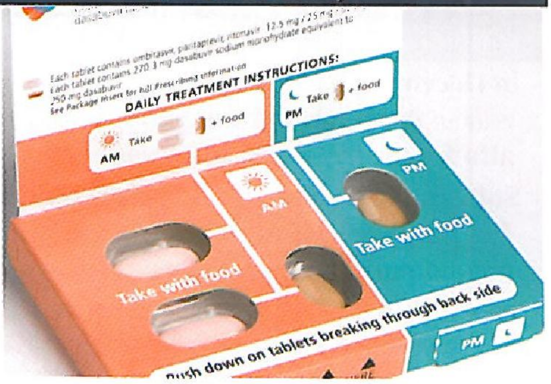
Ledipasvir/Sofosbuvir (Harvoni®)

- In **October 2014 FDA** was *approved* **Ledipasvir 90 mg/Sofosbuvir 400 mg** [le-DIP-as-vir & soe-FOS-bue-vir]. **Harvoni®** was *developed by* **Gilead Sciences, Inc.**
- ***Mechanism***; - **Ledipasvir** ***inhibits*** the **HCV NS5A protein** ***necessary for*** **viral replication.**
  - **Sofosbuvir** is a ***prodrug*** *converted to* **active form** (**GS-461203**), ***inhibits*** **NS5B RNA-dependent RNA** ***polymerase***, also ***essential for*** **viral replication**, and *acts as* a **chain terminator.**
- ***Dose***; **1 tablet** (**Ledipasvir 90 mg/Sofosbuvir 400 mg**) **orally** ***once*** **daily** *with* or *without* **food.**
- ***Therapy***; Used ***alone*** OR in ***combination*** *with* **Ribavirin** ***in*** **compensated cirrhosis patients.**
- ***Duration of therapy***; **8-12 weeks** (***without*** **cirrhosis**) or **24 weeks** (***with*** **compensated cirrhosis**).
- ***Response rates***; **95%.**
- ***Most Common side effects***; **Fatigue** and **headache.**
- ***Drug Interactions***; **Like** ***other*** **PIs**; **is** ***substrates*** for the **CYP3A4** *isoenzyme.*

Simeprevir (Olysio®) + Sofosbuvir (Sovaldi®)

- In **November 2014 FDA** was *approved* **Simeprevir** (Olysio®) **PLUS Sofosbuvir** (Sovaldi®) in ***combination*** for the ***treatment of*** **HCV** in people with **Genotype 1.**
- ***Therapy***; Used ***alone*** OR in ***combination*** *with* **Ribavirin** ***in*** **compensated cirrhosis patients.**
- ***Duration of therapy***; **12 weeks** (***without*** **cirrhosis**) or **24 weeks** (***with*** **compensated cirrhosis**).
- ***Response rates***; **95%.**

Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (Viekira Pak®)


DAILY TREATMENT INSTRUCTIONS:
AM
Take + food
PM
Take + food
AM
PM
Take with food
Take with food
Push down on tablets breaking through back side
PM

- In **December 2014 FDA** was *approved* **Ombitasvir/Paritaprevir/Ritonavir** [om-BIT-as-vir, PAR-i-TAP-re vir, and rye-TON-a-vir] **(12.5mg/75mg/50mg) + Dasabuvir (250mg)** [da-SAB-ue-vir] (Viekira Pak®) for the ***treatment of*** **HCV** in people with **Genotype 1.**
- ***Therapy***; Used ***alone*** OR in ***combination*** *with* **Ribavirin** ***in*** **compensated cirrhosis patients.**
- ***Duration of therapy***; **12 weeks** (***without*** **cirrhosis**) or **24 weeks** (***with*** **compensated cirrhosis**).
- ***Response rates***; **97%.**
- ***Mechanism***; *Combines* **3 Direct-Acting Antivirals (DAAs)**;
  1) **Ombitasvir** ***inhibits*** **HCV NS5A**, and interferes with viral RNA replication and virion assembly.
  2) **Paritaprevir** ***inhibits*** **HCV NS3/4A protease** and interferes with HCV coded polyprotein cleavage necessary for viral replication.
  3) **Dasabuvir** ***inhibits*** **HCV RNA-dependent RNA polymerase** (encoded by the **NS5B gene**) which is also necessary for viral replication.

  * **Ritonavir** is ***not active*** **against HCV. Ritonavir** is a ***potent*** **CYP3A inhibitor** that ***increases*** **peak** and trough plasma drug ***concentrations*** of **Paritaprevir** and overall drug exposure (***pharmacokinetic enhancer***).
- **Viekira XR®; Coformulated tablet** ***containing*** **Ombitasvir, Paritaprevir, Ritonavir** and **Dasabuvir** as a ***fixed-dose*** **combination** in **one tablet.**

Ombitasvir/Paritaprevir/Ritonavir (Qurevo®) (Technivie®)

- In **July 2015 FDA** was *approved* **Ombitasvir/Paritaprevir/Ritonavir (12.5mg/75mg/50mg)** for the ***treatment of*** **HCV** in people with **Genotype 4.**
- ***Therapy***; Used ***alone*** OR in ***combination*** *with* **Ribavirin** ***in*** **compensated cirrhosis patients.**
- ***Duration of therapy***; **12 weeks** (***without*** **cirrhosis**) or **24 weeks** (***with*** **compensated cirrhosis**).
- ***Response rates***; **100%.**
- *No* **dosage adjustment** required in ***mild, moderate***, or ***severe*** **renal impairment.**

Daclatasvir (Daklinza®) + Sofosbuvir (Sovaldi®)

- In **July 2015 FDA** was *approved* **Daclatasvir** [dak-LAT-as-vir] **(30mg - 60mg - 90mg)** for the ***treatment of*** **HCV** in people with **Genotype 1 or 3** in ***combination with*** **Sofosbuvir** (Sovaldi®), ***with*** or ***without*** **Ribavirin** (***this*** **regimen** are used in ***all*** **genotypes**). ***Response rates***; **97%.**
- **Daclatasvir** ***inhibits*** the **HCV NS5A protein** ***necessary for*** **viral replication.**

Elbasvir/Grazoprevir (Zepatier®)

- In January **2016 FDA** was ***approved*** **Elbasvir 50 mg** and **Grazoprevir 100 mg** [ELB-as-vir & graz-OH-pre-vir] **once *daily*** for the ***treatment of*** **HCV** in people with **Genotype 1 or 4, Zepatier®** was ***developed by*** **Merck.**
- ***Mechanism***; - **Elbasvir** is an **NS5A protein *inhibitor*.**
  - **Grazoprevir** is an **NS3/4A *inhibitor*.**
- ***Therapy***; **Used *alone*** OR in ***combination with*** **Ribavirin** if HCV RNA >800,000 IU/L.
- ***Duration of therapy***; **12 weeks** (most patient) or **16 weeks** (Genotype 1; PegIFN/RBV-experienced with baseline NS5A polymorphisms OR Genotype 4; PegIFN/RBV-experienced).

Sofosbuvir/Velpatasvir (Epclusa®)

- In June **2016 FDA** was ***approved*** **Sofosbuvir 400 mg** and **Velpatasvir 100 mg** [soe-FOS-bue-vir and vel-PAT-as-vir] **once *daily*** for the ***treatment of*** **HCV** in people with ***all*** **genotypes, Epclusa®** was ***developed by*** **Gilead Sciences, Inc.**
- ***Mechanism***; - **Sofosbuvir** is a ***nucleotide analog*** **HCV NS5B polymerase *inhibitor*.**
  - **Velpatasvir** is a **HCV NS5A *inhibitor*.**
- ***Therapy***; **Used *alone*** OR in ***combination with*** **Ribavirin** in **genotype 3** with **treatment *experienced*.**
- ***Duration of therapy***; **12 weeks** (most patient) or **24 weeks *without* Ribavirin** in **genotype 3** with **treatment *experienced*.**

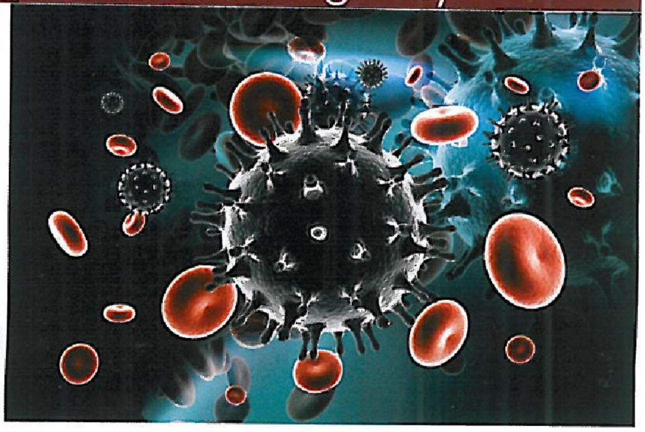
Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi®)

- In Jul **2017 FDA** was ***approved*** **Sofosbuvir/Velpatasvir/Voxilaprevir (400mg/100mg/100mg) *fixed-dose* combination** for ***treatment*** and ***re-treatment*** of **adults** with ***all*** **genotypes** of **HCV, Vosevi® (Gilead Triple Combo)** was ***developed by*** **Gilead Sciences, Inc.**
- ***Mechanism***; - **Sofosbuvir** is a ***nucleotide analog*** **HCV NS5B polymerase *inhibitor*.**
  - **Velpatasvir** is an **HCV NS5A *inhibitor*.**
  - **Voxilaprevir** is **HCV NS3/4A *inhibitor*.**
- ***Duration of therapy***; **12 weeks.**
- ***Black box warning***; ***Risk*** of **hepatitis B virus (HBV) *reactivation*.**

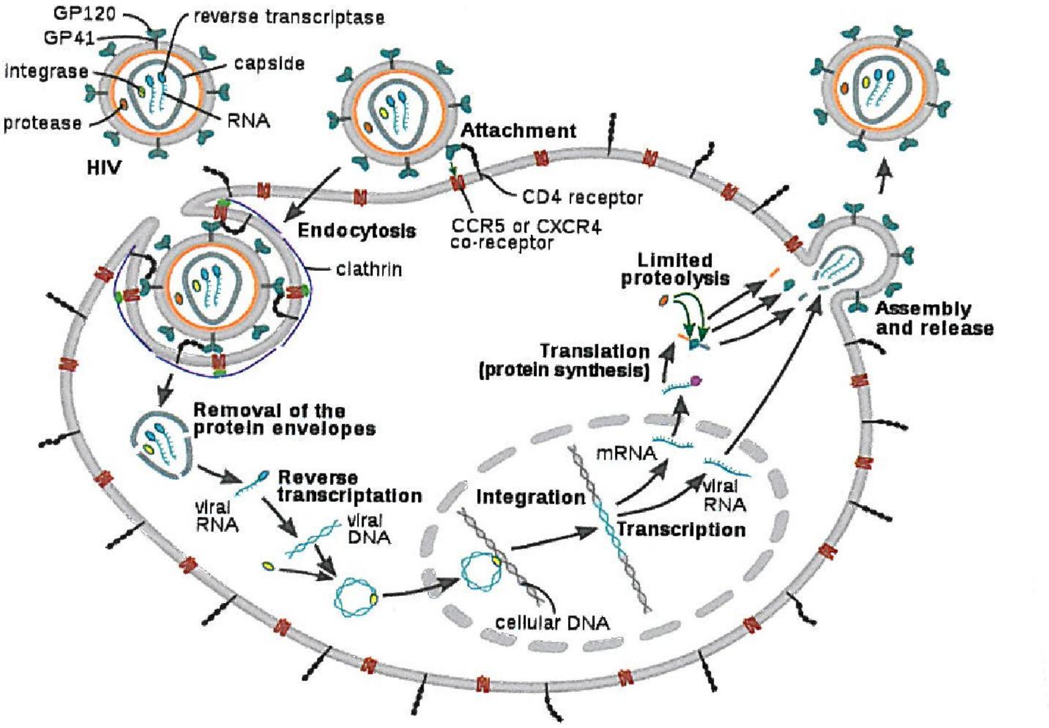
Glecaprevir/Pibrentasvir (Mavyret®)

- In Aug **2017 FDA** was ***approved*** **Glecaprevir/Pibrentasvir (100mg/40mg) *fixed-dose* combination** for ***treatment all*** **genotypes** of **HCV** in ***as short as*** **8 Weeks, Mavyret®** was ***developed by*** **AbbVie.**
- **Mavyret®** is **used** in ***all stages*** of **chronic kidney disease.**
- ***Dose***; **3 tablets** (300 mg/120 mg total dose) **orally once *daily with*** **food.**
- ***Duration of therapy***; - **8 weeks** if ***no*** **cirrhosis** and **12 weeks in cirrhosis.**
  - **16 weeks** in *some* **treatment-experienced patients** with **cirrhosis.**
- ***Mechanism***; - **Glecaprevir: HCV NS3/4A inhibitor.**
  - **Pibrentasvir: HCV NS5A inhibitor.**

Antivirals for HIV Infection (Antiretroviral Agents)

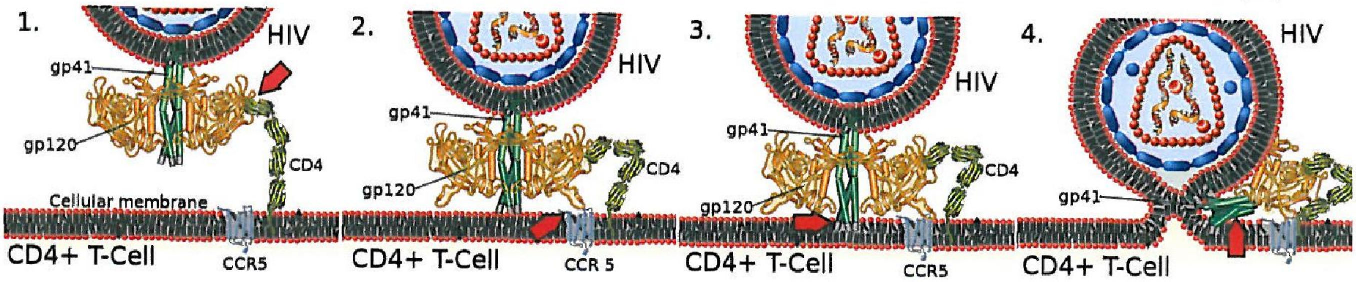


- The **Human Immunodeficiency Virus** (**HIV**) is a ***lentivirus*** (a *subgroup* of **Retrovirus**) that causes **HIV infection** & ***over time*** **Acquired Immunodeficiency Syndrome** (**AIDS**).
- **Infection** with **HIV** occurs by the ***transfer of*** **blood**, **pre-ejaculate**, **semen**, **vaginal fluids**, or **breast milk**.
- **HIV** ***infects*** **vital** **cells** in the ***human*** **immune system** such as ***helper*** **T cells** (*specifically* **CD4⁺ T cells**), **macrophages** & **dendritic cells**.
- **HIV infection** *leads to* ***low*** *levels* of **CD4⁺ T** **cells**, so ***cell-mediated*** **immunity** is ***lost***, and the **body** ***becomes*** progressively ***more susceptible*** to **opportunistic infections**.
- **AIDS** was ***first*** **clinically observed** in **1981** in the **United States**, and **virus** was named **AIDS Associated Retrovirus** (**ARV**) in **1983**.
- **Antiretroviral Drugs** are ***medications*** for the ***treatment*** of infection by **Retroviruses**, *primarily* **HIV**.
- **Zidovudine** was the ***first agent*** *approved in* **1987** for treatment of **HIV infections**.
- **Today**, the **viral life cycle** is ***understood***, and a ***combination*** of **drugs** is used to ***suppress*** **replication** of **HIV** and ***restore*** the **number** of **CD4⁺ T cells** and **immuno-competence** to the **host**.

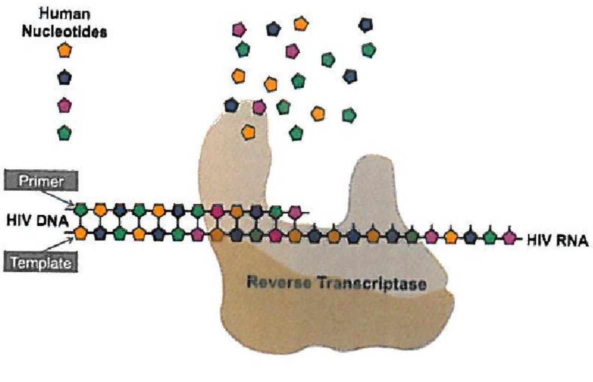

GP120
GP41
reverse transcriptase
integrase
capside
protease
RNA
HIV
Attachment
CD4 receptor
CCR5 or CXCR4 co-receptor
Endocytosis
clathrin
Limited proteolysis
Assembly and release
Translation (protein synthesis)
Removal of the protein envelopes
Reverse transcriptation
viral RNA
viral DNA
mRNA
Integration
viral RNA
Transcription
cellular DNA

1) Initial interaction between gp120 and CD4.
2) Conformational change in gp120 allows for secondary interaction with CCR5.
3) The distal tips of gp41 are inserted into the cellular membrane.
4) gp41 undergoes significant conformational change; folding in half and forming coiled-coils. This process pulls the viral and cellular membranes together, fusing them.

- ***Replication Cycle***;
  * **Adsorption** and **Entry**; The **HIV virion** ***enters*** **CD4⁺ T cells** (or **Macrophages**) by the ***adsorption*** of **glycoproteins** on its **surface** (**gp120**) to **CD4 receptors** (**high-affinity** ***attachment***), ***conformational*** **change** in **gp120** allows for ***secondary*** **interaction** with **CCR5**. **Clathrin-dependent endocytosis** of **HIV-1** is the *route of* ***productive*** **entry**.

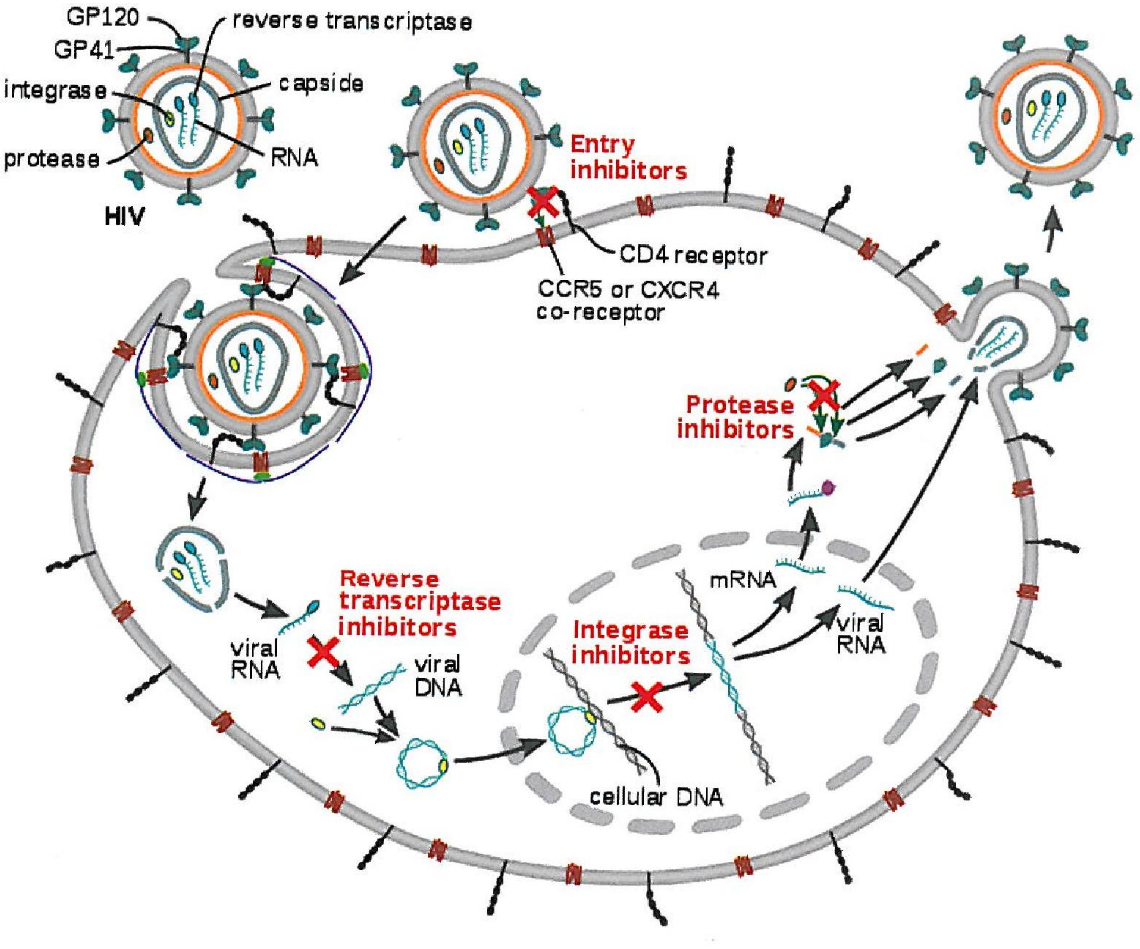

1.
HIV
gp41
gp120
CD4
Cellular membrane
CD4+ T-Cell
CCR5
2.
HIV
gp41
gp120
CD4
CD4+ T-Cell
CCR 5
3.
HIV
gp41
gp120
CD4
CD4+ T-Cell
CCR5
4.
HIV
gp41
CD4+ T-Cell

* **Replication** and **Transcription**;
  - ***Shortly* after** the **viral capsid** ***enters*** the **cell**, **reverse transcriptase** ***enzyme copies*** **single-stranded viral RNA** into a ***complementary*** **DNA (cDNA) molecule.**
  - The ***process*** of **reverse transcription** is ***extremely*** **error-prone**, and the ***resulting*** **mutations** (***very high*** **genetic** ***variability***) may cause **drug resistance** or ***allow*** the **virus** to ***evade*** the **body's immune system.**
  - The **reverse transcriptase** also has **ribonuclease *activity*** that **degrades** the **viral RNA** ***during*** the ***synthesis*** of **cDNA.**


Human Nucleotides
Primer
HIV DNA
Template
HIV RNA
Reverse Transcriptase

  - **Viral DNA** is ***transported*** into the **cell nucleus** and ***integrate*** into the **host cell's *genome*** by *another* **viral enzyme** called **integrase**. This ***integrated*** **viral DNA** *may then* **lie dormant**, in the **latent stage** of **HIV infection.**
  - To ***actively*** **produce** the **virus**, certain **cellular transcription factors** need to be ***present***, the ***most important*** of which is **NF-κB (NF kappa B)**, which is ***upregulated*** when **T-cells** become ***activated***;
    - i.e. **T-cells** that ***activated*** to ***fighting*** **HIV infection** are ***most likely*** to be **killed** by **HIV.**
  - The ***integrated*** **DNA** is ***transcribed into*** **viral RNA**, and **mRNAs** to ***translate into*** the **regulatory proteins.**
  - **HIV protease cleaves *newly*** **synthesized polyproteins** at the ***appropriate*** **places** to create the ***mature*** **protein components** of an ***infectious*** **HIV virion.**
  - ***Two*** **RNA genomes** are ***encapsidated*** in ***each*** **HIV virion.**

- ***Antiretroviral Agents***;
  * **Nucleoside/nucleotide Reverse Transcriptase Inhibitors (NRTIs).**
  * **Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs).**
  * **Protease Inhibitors (PIs).**
  * **Fusion Inhibitors.**
  * **CCR5 Receptor Antagonists.**
  * **Integrase Inhibitors.**

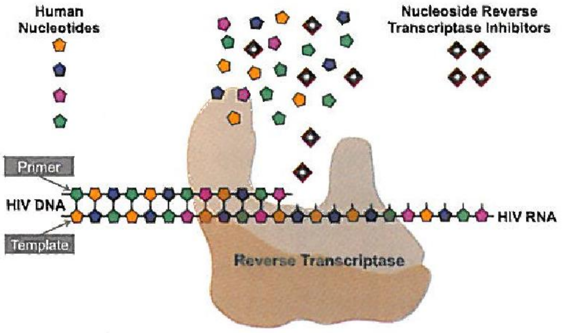

GP120
reverse transcriptase
GP41
integrase
capside
protease
RNA
HIV
Entry inhibitors
CD4 receptor
CCR5 or CXCR4 co-receptor
Protease inhibitors
Reverse transcriptase inhibitors
viral RNA
viral DNA
Integrase inhibitors
mRNA
viral RNA
cellular DNA

A) Nucleoside/nucleotide Reverse-Transcriptase Inhibitors (NRTIs)

- **Reverse Transcriptase Inhibitors** (**RTIs**) are a *class* of **Antiretroviral Drugs** used to *treat* **HIV infection** or **AIDS**, and in *some cases* **Hepatitis B**.
- **Nucleoside/nucleotide Reverse Transcriptase Inhibitors** (**NRTIs**) are *analogues* of the **naturally occurring deoxynucleotides** needed to *synthesize* the **viral DNA** and they *compete* with the *natural* **deoxynucleotides** for *incorporation* into the growing **viral DNA chain**.

Mechanism OF Action

- **NRTIs** are ***analogues*** of *native* **nucleosides** or **nucleotides**, which ***all*** **lack** a **3′-hydroxyl group** (*act as*; **Chain Terminators**).
- **Once** they *enter* **cells**, they are ***phosphorylated*** by **cellular enzymes** to the *corresponding* **triphosphate analog**, which is *preferentially* **incorporated** ***into*** the **viral DNA** by **reverse transcriptase**.
- *Because* the **3′-hydroxyl group** is ***not present***, a **3′,5′-phosphodiester bond** *between* an *incoming* **nucleoside triphosphate** and the *growing* **DNA chain** *cannot* be **formed** and **DNA chain elongation** is ***terminated***.



- ***Affinities*** of the **drugs** for ***many*** **host cell DNA polymerases** are ***lower than*** they are for **HIV reverse transcriptase**, although **mitochondrial DNA polymerase γ** appears to be ***susceptible*** at **therapeutic concentrations**.

Side Effects

- ***All*** **NRTIs** may be ***associated with*** **mitochondrial toxicity**, probably owing to *inhibition* of **mitochondrial DNA polymerase gamma**;
  - * **Toxicities** *such as* **peripheral neuropathy**, **pancreatitis** & **lipoatrophy**.
  - * **Dideoxynucleosides**, such as **Didanosine** and **Stavudine**, have a ***greater affinity*** for the **mitochondrial DNA polymerase**.
- ***All*** **NRTIs** have been ***associated with*** a ***potentially*** **fatal liver toxicity** ***characterized by*** **lactic acidosis** and **hepatomegaly** *with* **steatosis**.

Notes

- **NRTIs** are ***primarily*** **renally *excreted***, and ***all*** **require dosage adjustment** in **renal insufficiency** ***except*** **Abacavir**, which is ***metabolized by*** **alcohol dehydrogenase** and **glucuronyl transferase**.
- *Because* **cross-resistance** and **antagonism** *occur* ***between*** **agents** of the ***same*** **analog class** (**Thymidine**, **Cytosine**, **Guanosine** and **Adenosine**), ***concomitant use*** of **agents** with the ***same*** **analog** target is ***contraindicated*** (*for example*; **Zidovudine** and **Stavudine** are ***both*** **analogs** of **Thymidine** and ***should not*** be **used together**).

Zidovudine (ZDV) (Retrovir®)

- **Zidovudine** (**ZDV**) [zye-DOE-vyoo-deen] OR **Azidothymidine** (**AZT**) is a ***thymidine analog***, was the ***first agent available for*** the **treatment** *of* **HIV infection**.
- **Zidovudine** *penetrates* **CNS** *well*.
- ***Indications***; - ***Adult*** **HIV Infection**;
    - **Oral**: 300 mg orally every 12 hours or 200 mg orally every 8 hours.
    - **IV**: 1 mg/kg IV (infused over 1 hour) every 4 hours around the clock, total daily dose of 5-6 mg/kg.
  - ***Children*** **HIV Infection**.
  - **Prevent perinatal** (**fetal**) **transmission** of **HIV**.
  - **Non-occupational exposure** (***prophylaxis***) [*off-label*]; within 72 hours of exposure.
- **Zidovudine** is ***available*** in a ***fixed-dose*** **combination** ***formulation*** with **Lamivudine** (**Combivir®**), or with **Lamivudine** and **Abacavir** (**Trizivir®**).
- ***Both*** **Stavudine** and **Ribavirin** are ***activated by*** the same **intracellular pathways** and ***should not*** be **given** *with* **Zidovudine**.
- ***Common side effects***; **Anemia**, **Neutropenia**, **Headache** and **GI intolerance**.

Stavudine (d4T) (Zerit®)

- **Stavudine** [STAV-yoo-deen] is a ***thymidine analog***, ***approved for*** the **treatment** *of* **HIV infection**.
- ***Dose***; - Birth to 13 days: 0.5 mg/kg orally every 12 hours. - 14 days to < 30 kg: 1 mg/kg orally every 12 hours.
  - 30-60 kg: 30 mg orally every 12 hours. - ≥ 60 kg: 40 mg orally every 12 hours.
- **Stavudine** is a ***strong* DNA polymerases *inhibitor***, thus ***reducing* mitochondrial DNA synthesis** and ***resulting*** in **toxicity**.
- ***Side effects and toxicity***; **Headache**, **GI intolerance**, and **Peripheral Neuropathy**, **Pancreatitis**, **Lactic Acidosis** and **Hepatomegaly** *with* **Steatosis**.

Didanosine (ddI) (Videx®)

- **Didanosine** [dye-DAN-oh-seen] or **Dideoxyinosine** (**ddI**) is a ***deoxyadenosine analog***, it was the ***second drug***, ***approved for*** the **treatment** *of* **HIV infection**.
- ***Oral bioavailability*** is **low** (42%), **food *reduce* bioavailability** and ***should be*** **taken** on an **empty stomach** with **enteric-coated formulation** (*to prevent inactivation by gastric acid*).
- ***Dose***; *Delayed-release capsules*: - < 60 kg: 250 mg orally once a day - ≥ 60 kg: 400 mg orally once a day
- ***Toxicity***; ***Dose-dependent* Pancreatitis**, **Lactic Acidosis** and **Hepatomegaly** *with* **Steatosis** (drugs with the ***potential*** to **cause Pancreatitis**, *including* **Zalcitabine**, **Stavudine**, **Ribavirin**, and **Hydroxyurea**, ***should be avoided***).
- ***Side effects***; **Peripheral Neuropathy** and **Diarrhea**.

Abacavir (ABC) (Ziagen®)

- **Abacavir** (ABC) [a-BA-ka-veer] is a ***guanosine analog***, ***well* absorbed *orally*** (83%) and is ***unaffected*** by **food**.
- **Abacavir** ***should be*** used in **combination** in **HIV Infection** with ***other* antiretroviral agents**, **Abacavir** is ***available*** in a ***fixed-dose* combination *formulation***;
  - **Kivexa®**; **Abacavir/Lamivudine**.
  - **Triumeq®**; **Abacavir/Dolutegravir/Lamivudine**.
  - **Trizivir®**; **Abacavir/Lamivudine/Zidovudine**.
- **Abacavir** may be ***used*** in **non-occupational** and **occupational exposure**; within 72 hours of exposure.
- ***Dose***; 300 mg orally twice a day OR 600 mg orally once a day.
- ***Serious side effects***; **Hypersensitivity reaction**; **serious** and ***sometimes* fatal**.
- ***Common side effects***; **Headache, fatigue, nausea** and **vomiting**.
- ***Cautions***; **Abacavir *should be*** used ***cautiously*** in **patients** with ***existing* cardiac *risk factors*** due to a possible ***increased* risk *of* myocardial *events***.

Lamivudine (3TC) (Zeffix®)

- **Lamivudine** [la-MI-vyoo-deen] or **2′-deoxy-3′-thiacytidine** (3TC) is a ***cytidine analog*** used in **HIV Infection** and **chronic hepatitis B**.
- **Lamivudine** is ***typically* used** in **combination** with ***other* Antiretrovirals** like **Zidovudine** & **Abacavir**
- ***Dose***; 150 mg orally twice a day or 300 mg orally once a day.
- ***Side effects***; ***Excellent* safety profile** (Headache, nausea and dizziness are rare).
- ***Precautions***; **Lactic acidosis**, **hepatomegaly** and ***severe acute* Exacerbation** of **hepatitis B** *may result*.

Emtricitabine (FTC) (Emtriva®)

- **Emtricitabine** [em-tri-SIGH-ta-been], or **2',3'-dideoxy-5-fluoro-3'-thiacytidine** (**FTC**) is a ***fluoro derivative*** of **Lamivudine** used in **HIV Infection** and **chronic hepatitis B**.
- **Emtricitabine** is **used** in **combination**, ***typically with*** **Tenofovir** and ***other* Antiretrovirals**, ***like***; ***Integrase Inhibitors*** and **others**;
  - **Truvada®**; **Emtricitabine/Tenofovir**.
  - **Atripla®**; **Emtricitabine/Tenofovir/Efavirenz**.
  - **Complera®**, **Eviplera®**; **Emtricitabine/Tenofovir/Rilpivirine**.
  - **Stribild®**; **Emtricitabine/Tenofovir/Elvitegravir/Cobicistat**.
- ***Oral solution*** of **Emtricitabine** (and **Amprenavir**) ***contain* propylene glycol**; ***contraindicated*** in **pregnancy** and ***young* children** (< 4 years) and in **patients** with **hepatic** or **renal *dysfunction***.
- ***Dose***; 200 mg capsule orally once a day OR 240 mg (24 mL) oral solution orally once a day.
- ***Side effects*** and ***Precautions***; ***like* Lamivudine *in addition***, **Hyperpigmentation** of the **palms** or **soles** *may be* **observed**, ***particularly*** in **African-Americans**.

Tenofovir Disoproxil Fumarate (TDF) (Viread®)
Tenofovir Alafenamide (TAF) (Vemlidy®)

- **Tenofovir** [te-NOE-fo-veer] is **adenosine *analog*** used in **HIV Infection** and **chronic hepatitis B**.
- **Tenofovir** ***decreases*** the **concentrations** of the **Atazanavir** (*protease inhibitor*), **Atazanavir *must be boosted*** with **Ritonavir** if these **agents** are ***given*** **concurrently**.
- *Dose*; 300 mg orally once a day.
- **Tenofovir** is used in ***combination***, with **Emtricitabine** and **Efavirenz**;
  - **Truvada®**; **Emtricitabine/Tenofovir**.
  - **Atripla®**; **Efavirenz/Emtricitabine/Tenofovir**.
- *Side effects*; **Fatigue, diarrhea, nausea** and **pain**.
- *Precautions*; ***like*** **Lamivudine**.

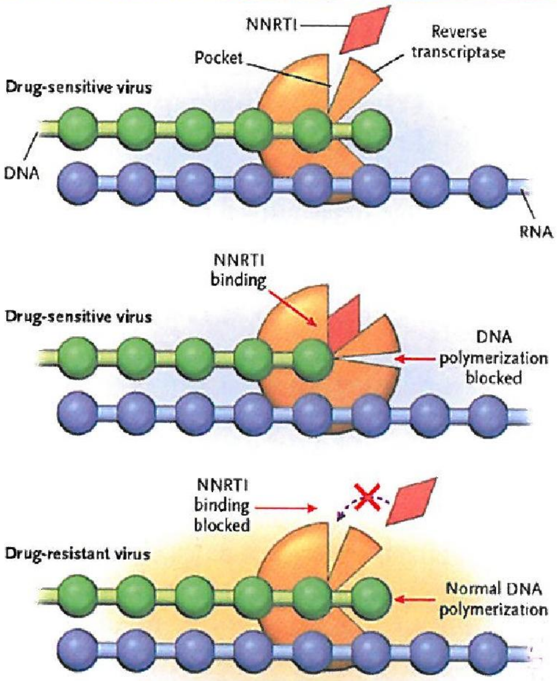
Zalcitabine (ddC) (Hivid®)

- **Zalcitabine** [zal-SITE-ah-been] or **2′-3′-dideoxycytidine** (**ddC**) is a ***cytosine analog*** and it was the ***third*** **antiretroviral** to be **approved** by the **FDA** for the ***treatment of*** HIV/AIDS.
- **Zalcitabine** has even been ***removed from*** **some countries** and ***less*** **used today**.

- **Amdoxovir**, **Apricitabine**, **Censavudine**, **Elvucitabine**, **Racivir** and **Stampidine** are ***other*** **Nucleoside/nucleotide Reverse Transcriptase Inhibitors** (**NRTIs**) in **clinical trials *undergoing* research** for the ***treatment of*** HIV/AIDS and/or **Hepatitis B virus**.

B) Non-nucleoside Reverse-Transcriptase Inhibitors (NNRTIs)

- **Non-nucleoside Reverse-Transcriptase Inhibitors** (**NNRTIs**) **bind *directly*** at an **allosteric hydrophobic site *adjacent*** to the **active site**, inducing a ***conformational*** **change** that ***results*** in **enzyme inhibition** and ***block*** **viral dependent DNA polymerase *activity***.
- ***Unlike*** the **NRTIs**, **NNRTIs *neither*** **compete** with **nucleoside triphosphates *nor require*** **phosphorylation** to be **active**.
- **NNRTI resistance** occurs ***rapidly*** with **monotherapy** and **can *result*** from a **single mutation**.
- ***All*** **NNRTIs** are ***substrates*** for **CYP3A4** and can ***act as inducers*** (**Nevirapine**), ***inhibitors*** (**Delavirdine**), or ***mixed inducers & inhibitors*** (**Efavirenz**, **Etravirine**).
- **NNRTIs** have ***common*** **characteristics** that include **cross-resistance** with ***other*** **NNRTIs**, **drug interactions**, and a ***high incidence*** of **hypersensitivity reactions**, *including* **rash**.



Efavirenz (EFV) (Sustiva®)

- **Efavirenz** [e-FA-veer-enz] is the ***preferred*** **NNRTIs**, ***widely*** **used** to ***treat*** and ***prevent*** **HIV/AIDS** in ***combination*** with ***other*** **antiretrovirals**; **Atripla®**; **Efavirenz/Emtricitabine/Tenofovir**.
- **Efavirenz** is a ***substrate of*** the **CYP450**;
  - ***Inhibits***: **CYP2C9**, **CYP2C19**, and **CYP3A4** (***in vitro***).
  - ***Induces***: **CYP3A4** (***in vivo***).
- *Dose*; **600 mg orally**, ***only*** on **empty stomach once daily *preferably*** at **bedtime** (*to reduce CNS side effects; toxicity may increase owing to increased bioavailability after a high-fat meal*).
- *Most common side effects*; **CNS side effects** (**dizziness**, **headache**, **vivid dreams**, **loss *of* concentration** and **depression**) and **skin rash**.
- *Other common side effects*; **Nausea**, **vomiting**, **diarrhea** and ***increase*** **total serum cholesterol**.

Nevirapine (NVP) (Viramune®)

- **Nevirapine** [ne-VYE-ra-peen] is **NNRTIs**, **used** to in **HIV/AIDS** in ***combination*** with ***other*** **antiretrovirals** in **adults** and **pediatric** (>15 days).
- **Nevirapine** also **used** in **prevention** of **maternal-fetal HIV transmission**: **200 mg *orally*** as a **single dose** at ***onset*** of **labor**, in ***combination*** with **IV Zidovudine**.
- **Nevirapine *highly* lipophilic agent**, its ***wide tissue* distribution**, including the **CNS**, **placenta** and **breast milk**.
- **Nevirapine** is an ***inducer*** of the **CYP3A4 *isoenzymes***.
- ***Limitations of Use***; **Nevirapine *should not*** be **initiated** in;

  "higher risk of hepatic events"

  - ***Adult*** **females** with **CD4$^+$ cell counts *greater than* 250 cells/mm^3**.
  - ***Adult*** **males** with **CD4$^+$ cell counts *greater than* 400 cells/mm^3**.
- ***Dose***; 200 mg orally once daily for the first 14 days, ***THEN***

  If no rash, increase to 200 mg twice daily; if rash occurs wait until it is resolved before increasing.
- **Black Box Warning**; **Skin reactions**, **Hepatotoxicity** and **Monitoring**.
  - ***Severe, life-threatening* skin reactions**; *including* **Stevens-Johnson syndrome** and **toxic epidermal necrolysis**.
  - ***Severe, life-threatening***, and in *some cases* ***fatal*** **hepatotoxicity**.
  - ***Monitoring***; ***during*** the ***first*** **18 weeks** of **therapy *essential***; ***extra*** **vigilance warranted** *during* ***first*** **6 weeks of therapy** (period of greatest risk).

Delavirdine (DLV) (Rescriptor®)

- **Delavirdine** [de-LA-vir-deen] is ***not recommended*** as a ***preferred*** or ***alternate*** **NNRTI** in the ***current*** **HIV guidelines**; **efficacy** is ***lower than other*** **NNRTIs** and ***inconvenient*** **dosing (3 times daily)**.

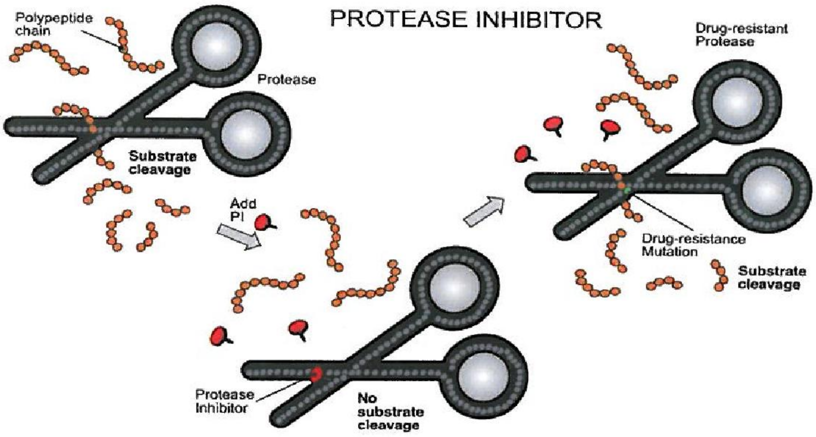
Etravirine (ETR) (Intelence®)

- **Etravirine** [et-ra-VYE-rine] was ***approved*** in **2008** as a ***second-generation*** **NNRTI** ***active against*** *many* **HIV strains** that are ***resistant*** to the ***first-generation*** **NNRTIs**.
- ***Bioavailability*** of **Etravirine *increased* 50%** *with* **food**.
- **Etravirine** is a ***substrate of*** the **CYP450**; - ***Inhibits***: **CYP2C9**, **CYP2C19** - ***Induces***: **CYP3A4**.
- ***Dose***; 200 mg twice daily.
- ***Most common side effects***; **Rash**, **Nausea** and ***Increased*** **LDL**.

Rilpivirine (RPV) (Edurant®)

- **Rilpivirine** [ril-pi-VIR-een] was ***approved*** in **2011** as a ***second-generation*** **NNRTI** for **HIV treatment-naïve patients** in ***combination*** with ***at least*** **2 *other*** **antiretroviral agents**.
- N.B.; ***Second-generation*** **NNRTIs** are ***higher*** **potency**, ***longer*** **half-life** and ***reduced*** **side-effect profile**.
- ***Bioavailability*** of **Rilpivirine *increased* 40%** *with* **food**.
- **Rilpivirine** has **pH-dependent *absorption*** (avoid co-administered with acid suppression therapy and antacids and requires dose separation).
- **Odefsey®**; A ***newer*** **fixed-dose *combination*** was ***approved*** in **2016**; **Rilpivirine/Emtricitabine/ Tenofovir Alafenamide**.
- ***Dose***; 25 mg once daily with meal.
- ***Most common side effects***; **Depression**, **headache**, **drowsiness** and **rash**.
- **Doravirine** is a ***second-generation*** **NNRTI** under ***development by*** **Merck & Co** for **HIV/AIDS**.

C) Protease Inhibitors (PIs)



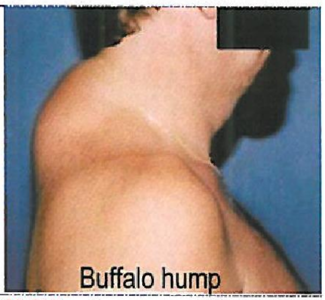
- **Protease inhibitors** (**PIs**) are a class of **antiviral drugs** that are ***widely used*** to treat **HIV/AIDS** and **hepatitis C**.
- **Hepatitis C virus NS3/4 protease inhibitors**; *class stem* **–previr** (**Boceprevir**, **Telaprevir**, **Simeprevir**, **Grazoprevir** and **Paritaprevir**)
- **Antiretroviral HIV protease inhibitors**; *class stem* **–navir**.
- **Protease inhibitors** ***prevent*** **viral replication** by ***selectively*** **binding to viral proteases** and ***blocking*** **proteolytic** ***cleavage*** of **protein** ***precursors*** that are ***necessary for*** the **production** of ***infectious*** **viral particles**.

Pharmaco Kinetics

- **Absorption**; ***High-fat*** **meals**;
  - ***Increase*** **bioavailability** of *some* **PIs**, such as **Nelfinavir** & **Saquinavir**
  - ***Decrease*** **bioavailability** of *some* **PIs**, such as **Indinavir**.
  - ***Other*** **PIs** are ***unaffected***.
- ***All*** **PIs** are ***substrates for*** **CYP3A4** and ***other*** **CYP450** ***isoenzymes***.
- ***Excretion***; ***very little*** **PIs** are ***excreted*** **unchanged** in **urine**; **NO dose** ***adjustments*** in **renal impairment**.

Side Effects

- **Nausea**, **vomiting** and **diarrhea**.
- ***Disturbances*** in **glucose** and **lipid metabolism**; ***including*** **diabetes**, **hypertriglyceridemia** and **hypercholesterolemia**.
- ***Chronic therapy*** results in **fat** ***redistribution***, *including* ***loss*** of **fat** *from* the **extremities**, **fat** ***accumulation*** in the **abdomen** and the ***base of*** the **neck** (**buffalo hump**) & **breast enlargement**.



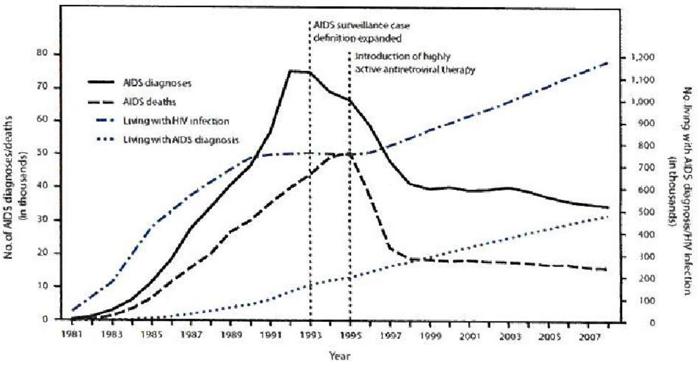
Buffalo hump

Drug Interactions

- **Drug interactions** are a ***common*** **problem** for ***all*** **PIs**, because they are ***not only*** **substrates** ***but also potent*** **inhibitors** of **CYP450** ***isoenzymes***.
- *For example* **dangerous interactions** ***with*** **PIs** *include*;
  - **Rhabdomyolysis** from **Simvastatin** or **Lovastatin**.
  - **Excessive sedation** from **Midazolam** or **Triazolam**.
  - **Respiratory depression** from **Fentanyl**.
- **CYP450** ***inducers*** may ***decrease*** **PI** ***plasma concentrations***, *contributing* to **treatment** ***failures***.

Ritonavir (RTV) (Norvir®)

- **Ritonavir** [ri-TOE-na-veer] is ***widely*** **used** *as* a **Pharmacokinetic Enhancer** or "***booster***" of ***other*** **PIs**.
- ***Mechanism***; **Ritonavir** is a ***potent*** **inhibitor** of **CYP3A**, and ***concomitant*** **Ritonavir** *administration* at *low* **doses** ***increases*** the ***bioavailability*** of the ***second*** **PI**, often *allowing for* ***longer*** **dosing intervals**; - **Kaletra®**; **Lopinavir/Ritonavir**; in **HIV/AIDS**.
  - **Qurevo®**; **Ombitasvir/Paritaprevir/Ritonavir**; in **hepatitis C**.
- **Ritonavir** as a ***booster*** also *help to* ***prevent*** the **development** of **resistance** and ***preferred*** **agents** in the **HIV treatment guidelines**.
- **Ritonavir** is approved by FDA in **1996**, making it the **7th** *approved* **antiretroviral drug** and the **2nd** *approved* **protease inhibitor** in the United States after **Saquinavir**, ***Within*** **2** years of the approval of **Ritonavir** and **Saquinavir** the **U.S. HIV-associated death** ***rate*** **fell** *from* ***over*** **50,000** *per* **year** *to* about **18,000**.



Saquinavir (SQV) (Invirase®)

- **Saquinavir** [sa-KWIH-na-veer] was the ***first*** **protease inhibitor** {1995} (and **6th antiretroviral**) **used *together*** with **Ritonavir** or **Lopinavir/Ritonavir** (to increase its effect) to ***treat*** or ***prevent*** **HIV/AIDS.**
- ***Absorption***; ***poor***; ***increased*** with ***high* fat meal.**
- Fortovase®, a soft gel capsule (micro-emulsion, orally-administered formulation) reformulated for improved bioavailability (8 fold more active drug than Invirase®) which was discontinued worldwide in 2006.
- ***Usual dosage***; **1000 mg *twice* daily** given in ***combination with* Ritonavir 100 mg *twice* daily.**
- **Saquinavir** may be ***associated with* QT** and **PR interval *prolongation*** (**ECG *should be* done** *prior to* ***starting*** **therapy**).

Indinavir (IDV) (Crixivan®)

- **Indinavir** [in-DIH-na-veer] has ***shortest*** **half-life** and ***latest*** **protein bound** of ***all*** **PIs**, so it ***wears off*** **quickly *after*** **dosing** and *requires* ***very*** **precise dosing *every* 8 hours** to ***thwart*** HIV from ***forming*** **drug-resistant mutations**; ***boosting*** with **Ritonavir *overcomes*** this **problem** and also ***permits*** **twice-daily *dosing*.**
- ***Absorption***; - ***Decreased*** *with* **meals**, ***even*** **light** or **low-fat snack** (***must be*** **taken** on an ***empty*** **stomach**).
  - **Acidic gastric *conditions*** are **necessary** *for* **absorption.**
- **Indinavir *characteristically*** causes **Nephrolithiasis/Urolithiasis** and **Hyperbilirubinemia.**
- ***Precautions***; ***Adequate*** **hydration** (at least 1.5 L of water per day) is **important** to ***reduce*** the **incidence** of **kidney stone formation.**
- **Indinavir** is being ***replaced by*** **newer drugs** that are ***more*** **convenient** to **take** and ***less likely*** to ***promote*** **virus resistance**, such as **Darunavir** or **Atazanavir.**

Nelfinavir (NFV) (Viracept®)

- **Nelfinavir** [nel-FIN-a-veer] ***should be*** **taken *with* food** (bioavailability increased 2.5 to 5 times).
- **Nelfinavir** is the ***only*** **PI** that ***cannot*** be **boosted** by **Ritonavir** (not extensively metabolized by CYP3A).
- ***Dose***; 750 mg 3 times daily or 1250 mg twice daily with meals in combination with other antiretroviral therapies.
- **Nelfinavir *characteristically*** causes **Diarrhea**; **Food** also ***decreases*** the **risk** of **diarrhea.**
- **Nelfinavir** has been ***under investigation*** for ***potential use*** as an **anti-cancer agent**; ***off-label used*** in **Multiple Myeloma.**

Amprenavir (Agenerase®)

Fosamprenavir (FPV) (Lexiva®)

- **Fosamprenavir** [fos-am-PREN-a-veer] is a ***prodrug*** of **Amprenavir** [am-PREN-ah-veer], with ***improved*** **pharmacokinetic parameters** and **dosing *regimen*** (slow-release **Amprenavir**).
- **Fosamprenavir** was ***approved*** by **FDA** in **2003** and ***production of*** **Amprenavir** was ***discontinued by*** the **manufacturer** in **2004.**
- **Fosamprenavir** is **used** in ***combination***, ***typically*** with ***low-dose*** **Ritonavir** or ***other*** **antiviral drugs.**
- ***Dose***; ***Adult***; 1,400 mg once daily ***without*** **Ritonavir** OR ***with*** **Ritonavir** 100 or 200 mg once daily.
- ***Most common side effects***; **Nausea, diarrhea, fatigue** and **rash.**

Lopinavir/Ritonavir (LPV/r) (Kaletra®)

- **Lopinavir** [loe-PIN-a-vir] has ***very poor*** **bioavailability**, which is ***enhanced by low-dose*** **Ritonavir.**
- **Lopinavir** is **used** in ***treatment*** and **nonoccupational postexposure *prophylaxis*** (off-label) of **HIV infection** in **adults** and **pediatric patients** > 14 days in ***combination with*** *other* **antiretroviral agents.**
- ***Dose***; - ***Twice***; **Lopinavir** 400 mg/**Ritonavir** 100 mg ***twice*** daily in naïve or therapy-experienced
  - ***Once***; **Lopinavir** 800 mg/**Ritonavir** 200 mg ***once*** daily in naïve or therapy-experienced *with* <3 Lopinavir resistance-associated substitutions.
    - * **Once-daily dosing** is ***not recommended*** in those ***receiving*** **Efavirenz**, **Fosamprenavir**, **Nevirapine**, **Nelfinavir**, **Carbamazepine**, **Phenobarbital** or **Phenytoin** (***induce*** **Lopinavir *metabolism***).
- A **2014 study *indicates*** that **Lopinavir** is ***effective against*** the **Human Papilloma Virus** (HPV).
- ***Most common side effects***; **Diarrhea, nausea, rash, hyperlipidemia** and **ALT increased.**

* ***History***;

- Research aimed at development of renin inhibitors as potential antihypertensive agents had led to the discovery of compounds that blocked the action of this peptide cleaving enzyme. The amino acid sequence cleaved by renin was found to be fortuitously the same as that required to produce the HIV peptide coat.
- Structure–activity studies on renin inhibitors proved to be of great value for developing HIV protease inhibitors.

Atazanavir (ATV) (Reyataz®)

- **Atazanavir** [ah-ta-ZA-na-veer] is a ***second generation* PIs** (***preferred* PIs**); ***Azapeptide* PI** with a **pharmacokinetic profile** that allows **once-daily *dosing***.
- ***Absorption***; - It ***should be*** **taken *with*** a **light meal** (*to enhance bioavailability*).
  - **Acidic gastric *conditions*** are **necessary *for* absorption**.
- **Atazanavir** is **used** in **HIV infection** in **naïve** or **experienced patients** and ***during* pregnancy** and **postpartum period**.
- ***Usual dosage***; **Naïve patients**; - **Atazanavir** 300 mg orally with 100 mg **Ritonavir** orally once a day.
  - If ***unable*** to tolerate **Ritonavir**; **Atazanavir** 400 mg orally once a day.
  - If ***used*** with **Efavirenz**: **Atazanavir** 400 mg + **Ritonavir** 100 mg orally once.
- In **Experienced patients**; If used with ***both*** an **H_2-receptor antagonist** and **Tenofovir**: **Atazanavir *must be* boosted**; **Atazanavir** 400 mg + **Ritonavir** 100 mg orally once a day.
- **Evotaz®**; **Atazanavir/Cobicistat** [**Cobicistat** is **Ritonavir *analog***]
- **Atazanavir *exhibits*** a ***decreased* risk** of **hyperlipidemia *compared with other* PIs**.
- **Atazanavir *characteristically*** causes **hyperbilirubinemia** and **jaundice**; **Atazanavir** is a ***competitive* inhibitor** of **glucuronyl transferase**.

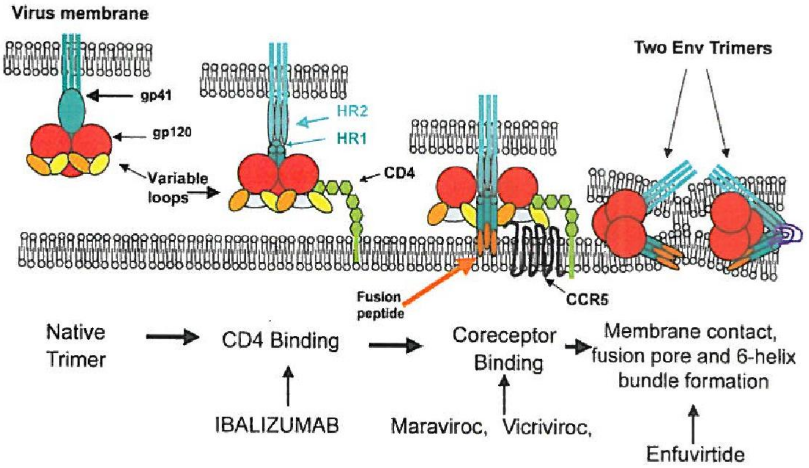
Tipranavir (TPV) (Aptivus®)

- **Tipranavir** [ti-PRA-na-veer] is a ***second generation* PIs**; **non-peptide PI** that **used** in **HIV *resistant to*** the ***other* PIs**.
- **Tipranavir** is **used *with* Ritonavir** in ***combination therapy*** to treat **HIV infection**.
- **Tipranavir** is ***useful*** in **"salvage" regimens** in **patients *with* multidrug resistance**.
- ***Dose***; **Tipranavir** 500 mg + **Ritonavir** 200 mg orally twice a day.
- **Black Box Warning**;
  - **Hepatotoxicity**; Some fatalities, have been reported (more common in patients with chronic HBV or HCV).
  - **Intracranial Hemorrhage**; Both fatal and non-fatal intracranial hemorrhage have been reported.

Darunavir (DRV) (Prezista®)

- **Darunavir** [da-RU-na-veer] is a ***second generation* PIs**; ***like* Tipranavir** they are **used** in **HIV *resistant to*** the ***other* PIs**.
- **Darunavir** is often **used** with ***low doses*** of **Ritonavir** or **Cobicistat** (**Ritonavir *analog***) to increase **Darunavir *levels***; **Prezcobix®**; **Darunavir/Cobicistat**.
- ***Bioavailability***: ***with* Ritonavir**: 82% - ***without* Ritonavir**; 37%.
- ***Dose***; - **Treatment-naive** or **-experienced**; 800 mg once daily with **Ritonavir** 100 mg or **Cobicistat** 150 mg once.
  - **Treatment-experienced** *with* **≥1 Darunavir resistance-associated** substitution; 600 mg twice daily with **Ritonavir** 100 mg twice daily.
- **Darunavir *contains*** a **sulfonamide *moiety*** and ***should be*** used ***cautiously*** in **patients *with* sulfonamide allergy**.
- ***Most common side effects***; **Nausea, diarrhea, headache** and **rash**.

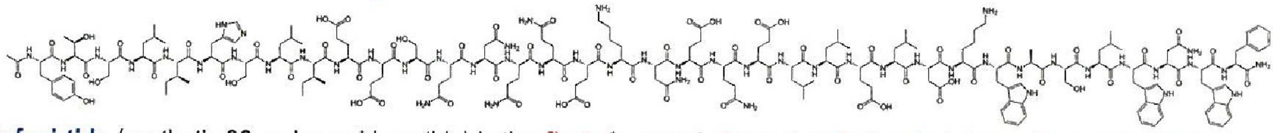
D) Entry/fusion Inhibitors



- **HIV** ***attachment*** to the **host cell** *entails* ***binding*** of the **viral envelope glycoprotein complex gp160** (consisting of **gp120** and **gp41**) to its **cellular receptor CD4**.
- This *binding* induces **conformational changes** in **gp120** that ***enable*** **access** to the ***chemokine receptors*** **CCR5** or **CXCR4**.
- **Chemokine receptor** ***binding*** *induces* ***further*** **conformational changes** in **gp120**, allowing ***exposure to*** **gp41** and ***leading to*** **fusion** of the **viral envelope** with the **host cell membrane** and subsequent **entry** of the **viral core** into the **cellular** ***cytoplasm***.

Enfuvirtide (Fuzeon®)

- **Enfuvirtide** [en-FU-veer-tide] is an **HIV fusion** ***inhibitor***.



Enfuvirtide (synthetic 36-amino-acid peptide) is the ***first*** of a **novel class** of **antiretroviral drugs** (**fusion** ***inhibitors***) used in ***combination therapy*** for the treatment of **HIV infection** *developed by* **Roche** (was approved by FDA in 2003)

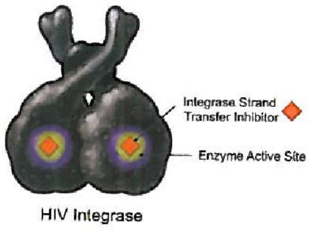
- ***Mechanism***; **Enfuvirtide** ***binds*** to the **gp41 subunit** of the **viral envelope glycoprotein**, ***preventing*** the **conformational changes** ***required for*** the **fusion** of the **viral** and **cellular membranes**.
- **Enfuvirtide** ***must be administered by*** **SC injection** (is the ***only*** **parenterally antiretroviral agent**).
- ***Resistance*** to **Enfuvirtide** can result from ***mutations*** in **gp41**.
- ***Dose***; 90 mg SC every 12 hours.
- **Enfuvirtide** ***must be*** **reconstituted** *for* **10 seconds** and ***roll*** *gently* ***between*** the **hands** to ***avoid*** **foaming** and to ***ensure*** *contact with* **diluent**.
- ***Most common side effects***; **injection site** ***reactions***, **diarrhea, nausea, fatigue, insomnia** and **peripheral neuropathy**.

Maraviroc (Selzentry®) (Celsentri®)

- **Maraviroc** [ma-RAV-i-rok] is a **CCR5 receptor** ***antagonist*** used in the ***treatment*** of **HIV infection**.
- **Maraviroc** is **used** ***only*** in the **HIV strains** of that ***use*** **CCR5** to ***gain*** **access** to the **cell**; **CCR5-tropic HIV-1 infection** (***not*** **against HIV strains** *with* **CXCR4**).
- ***Dose***; 300 mg orally twice daily.
- **Maraviroc** is ***metabolized*** by **CYP450**, and the ***dose must be*** **adjusted** when given with ***strong*** **CYP450** ***inhibitors*** (150 mg twice) or ***strong*** **CYP450** ***inducers*** (600 mg twice).
- ***Side effects***; **Upper respiratory** ***infections***, **cough, arthritis, rash** and **fever**.
- **Black Box Warnings**; ***Risks of*** **hepatotoxicity**.

- **Cenicriviroc** and **Vicriviroc** are ***other*** **CCR5 receptor** ***antagonist***; in **clinical trials**.
- **Ibalizumab** (**TNX-355**) is a **non-immunosuppressive** ***monoclonal antibody*** that ***binds*** **CD4**, ***inhibits*** the **HIV viral** ***entry***; in **clinical trials**.
- **PRO 140** is a ***humanized monoclonal antibody*** targeted ***against*** the **CCR5** ***receptor***; in **clinical trials**.
- **Fostemsavir** is an **HIV** ***entry inhibitor*** and a ***prodrug*** of **Temsavir**; in **clinical trials**.
- **VIR-576** is a ***synthesized*** **peptide** which ***binds*** to **gp41**, ***preventing*** **fusion**; in **clinical trials**.

E) Integrase Strand Transfer Inhibitors (INSTIs)



- **Integrase Strand Transfer Inhibitors (INSTIs)**, *often called* **Integrase Inhibitors (INIs)**, *work by* ***inhibiting*** the **insertion** of **viral DNA** ***into*** the **host cell DNA**.
- The **active site** of the ***integrase enzyme*** **binds** to the **host cell DNA** and ***includes*** **two divalent metal** ***cations*** that ***serve as*** **chelation targets** for the **INSTIs**.
- ***Drug interactions***; It is *therefore* **INSTI** ***doses*** are ***separated from*** **Antacids** and ***other*** **polyvalent cations** (**Magnesium**, **Calcium** and **Iron**) by ***several*** **hours**.
- ***Resistance*** to **INSTIs** occurs with ***single-point*** **mutations** ***within*** the **integrase gene**.
- ***Cross-resistance*** ***between*** **Raltegravir** and **Elvitegravir** *can occur*, although **Dolutegravir** has ***limited*** **cross-resistance** to ***other*** **INSTIs**.
- ***Most common side effects***; **Nausea** and **diarrhea**.

Raltegravir (RAL) (Isentress®)

- **Raltegravir** [ral-TEG-raveer] is the ***first*** of a ***new class*** (**Integrase Inhibitors**) of **HIV drugs**, was ***approved*** in **2007** for both ***initial therapy*** of **treatment-naïve patients** and **treatment-experienced patients in** ***combination*** with ***other*** **Antiretroviral agents**
- ***Formulations***; is ***available*** in **tablets** for ***adults*** and **chewable tablets** and **suspension** for **use** *in* ***children*** **2-11 years old**.
- ***Metabolism***; ***by*** **glucuronidation** and ***does not*** **interact** with the **CYP450** ***system***;
  - **N.B**; ***With*** **Rifampicin**, a ***strong inducer*** of **UDP-glucuronosyl transferase 1A1** (**UGT1A1**), the dose of **Raltegravir** should be ***increased*** from **400 mg** *twice* daily to **800 mg** twice daily.
- ***Usual Adult Dose***; 400 mg orally twice a day.
- ***Common side effects***;
  - **Nausea**, **diarrhea**, **headache fatigue** and **insomnia**.
  - ***Increases*** in ***serum*** **AST**, **glucose** and **bilirubin**.
  - ***Increases*** in **creatine kinase** *may occur*.
  - ***Potential*** **myopathy** or **rhabdomyolysis**.

Elvitegravir (EVG) (Vitekta®)

- **Elvitegravir** [el-vi-TEG-ra-vir] is an ***integrase inhibitor***, was ***developed by*** the **Gilead Sciences** and ***approved by*** the **US FDA** in **2012**.
- **Elvitegravir** is ***currently only*** **available** in a **fixed-dose** ***combination*** ***single tablet*** **Stribild®** and **Genvoya®** *developed by* the **Gilead Sciences** ***containing***;
  - **Stribild®**; **Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate**.
  - **Genvoya®**; **Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide**.
- **Elvitegravir** is ***metabolized by*** **CYP3A** and **Glucuronidation**.
- ***Half-life*** of **Elvitegravir** ***increased*** by **Cobicistat** (***booster***).

Dolutegravir (DTG) (Tivicay®)

- **Dolutegravir** [doe-loo-TEG-ra-vir] is an ***integrase inhibitor***, was ***developed by*** the **GSK** and ***approved by*** the **FDA** in **2013**.
- **Dolutegravir** is ***metabolized by*** **Glucuronidation** and ***minor*** *contributions* from **CYP3A**.
- **Dolutegravir** can be given ***once*** **daily** ***without*** the **use** of a **booster**, **but** ***must be*** given in ***combination*** with ***other*** **antiretroviral agents**.
- **Patients** with **Raltegravir** and **Elvitegravir** **resistance** ***mutations*** ***maintain*** **susceptibility** ***to*** **Dolutegravir**.

- **BI 224436**, **Bictegravir** (**GS-9883**), **Cabotegravir** and **MK-2048** are an ***integrase inhibitor***; in **clinical trials**.

➢ Antiretroviral Guidelines:-

Panel on Antiretroviral Guidelines for Adults and Adolescents

(Last reviewed October 17, 2017)

A) Recommended Initial Regimens for Most People with HIV (Naïve Patient);

- **Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors**;
  - **Dolutegravir + Abacavir/Lamivudine**
  - **Dolutegravir + Tenofovir/Emtricitabine**
  - **Elvitegravir-Cobicistat + Tenofovir/Emtricitabine**
  - **Raltegravir + Tenofovir/Emtricitabine**

B) Recommended Initial Regimens in Certain Clinical Situations;

- **Boosted Protease Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors**;
  - **Darunavir-Ritonavir (OR -Cobicistat) + Tenofovir/Emtricitabine**
  - **Atazanavir-Ritonavir (OR -Cobicistat) + Tenofovir/Emtricitabine**
  - **Darunavir-Ritonavir (OR -Cobicistat) + Abacavir/Lamivudine**; if HLA-B*5701 negative
  - **Atazanavir-Ritonavir (OR -Cobicistat) + Abacavir/Lamivudine**; if HLA-B*5701 negative and HIV RNA <100,000 copies/mL
- **Non-Nucleoside Reverse Transcriptase Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors**;
  - **Efavirenz + Tenofovir/Emtricitabine**
  - **Rilpivirine + Tenofovir/Emtricitabine**; if HIV RNA <100,000 copies/mL & CD4 count >200 cells/mm^3
- **Integrase Strand Transfer Inhibitors + 2 Nucleoside Reverse Transcriptase Inhibitors**;
  - **Raltegravir + Abacavir/Lamivudine**; if HLA-B*5701 negative and HIV RNA <100,000 copies/mL

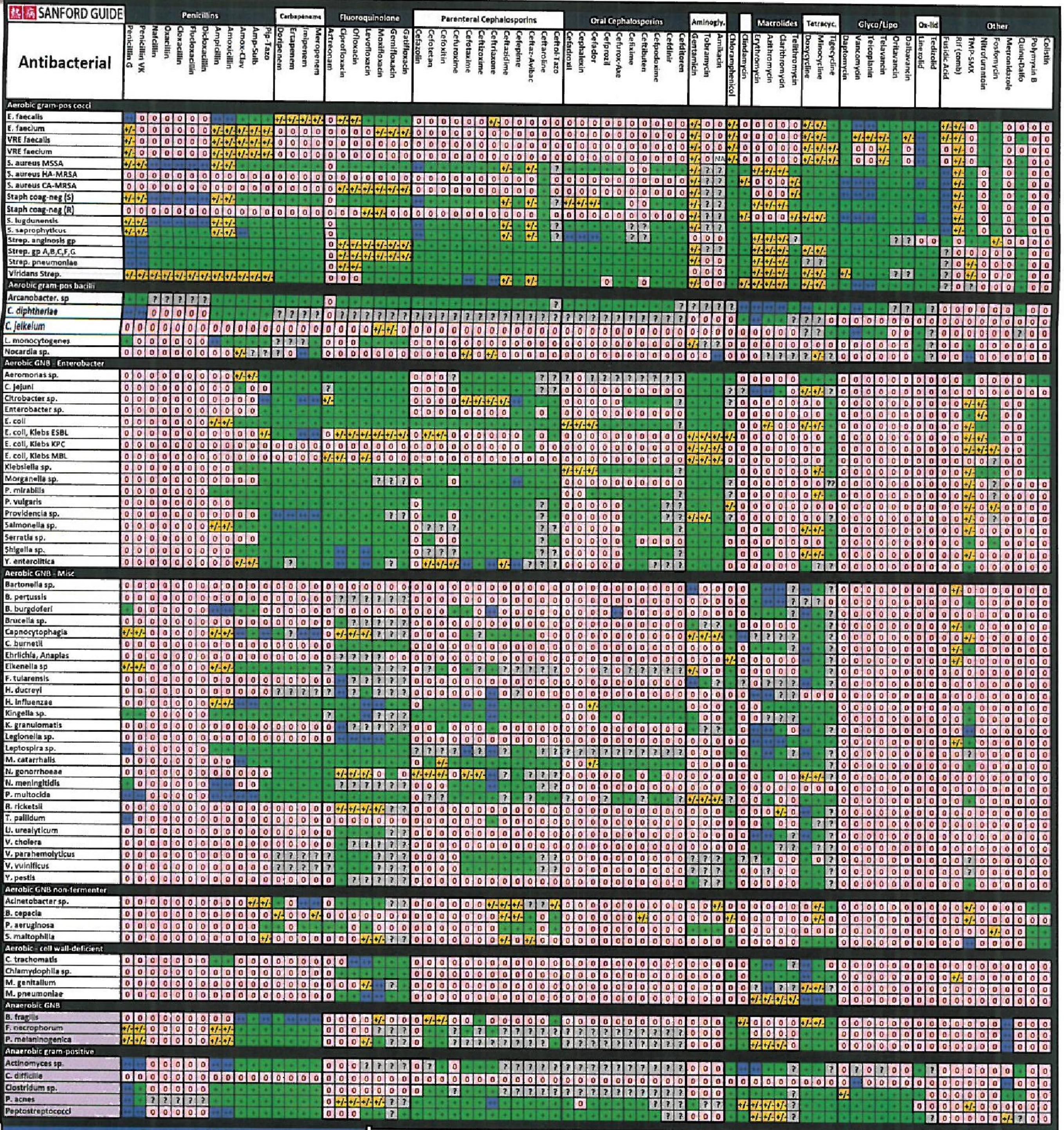
* **Regimens to Consider when Abacavir and Tenofovir Cannot be Used**:
  - **Darunavir-Ritonavir + Raltegravir**; if HIV RNA less than 100,000 copies/mL & CD4 >200 cells/mm^3
  - **Lopinavir-Ritonavir + Lamivudine**

C) Guidelines Recommendations for HIV Post-Exposure Prophylaxis (PEP); **PEP regimen**;

- The **preferred PEP regimen** are;
  - **CDC Recommendations (2013)**: **Tenofovir Disoproxil Fumarate** 300 mg orally daily + **Emtricitabine** 200 mg PO daily (**Truvada®**) PLUS **Raltegravir** (**Isentress®**) 400 mg orally twice daily.
  - **New York State Department of Health AIDS Institute (NYSDOH AI) Recommendations (2014)**; **Tenofovir Disoproxil Fumarate** 300 mg orally daily + **Emtricitabine** 200 mg orally daily OR **Lamivudine** 300 mg orally daily PLUS **Raltegravir** 400 mg orally twice daily OR **Dolutegravir** 50 mg orally daily.
- The ***first dose should*** be **given *as soon as* possible *after* exposure, *within* 72 hours** of ***exposure, ideally within* 2 hours *should not*** be **delayed** while ***awaiting*** the **results** of a **source patient's HIV test**.
- **HIV Antibody Testing**; at **baseline, 4 weeks** and **12 weeks** and **6 months *post-exposure***.

➢ Common Fixed-dose Combination Brands:-

Truvada®	**Emtricitabine/Tenofovir**
Kaletra®	**Lopinavir-Ritonavir**
Kivexa®	**Abacavir/Lamivudine**
Dutrebis®	**Raltegravir/Lamivudine**
Evotaz®	**Atazanavir-Cobicistat**
Prezcobix®	**Darunavir-Cobicistat**
Combivir®	**Lamivudine/Zidovudine**
Trizivir®	**Abacavir/Lamivudine/Zidovudine**
Atripla®	**Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate**
Complera®	**Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate**
Eviplera®	**Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate**
Odefsey®	**Rilpivirine/Emtricitabine/Tenofovir Alafenamide**
Triumeq®	**Dolutegravir/Abacavir/Lamivudine**
Stribild®	**Elvitegravir-Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate**
Genvoya®	**Elvitegravir-Cobicistat/Emtricitabine/Tenofovir Alafenamide**



SANFORD GUIDE Antibacterial

Recommended (++)
Agent is a first line therapy: reliably active in vitro, clinically effective, guideline recommended, recommended as a first-line agent or acceptable alternative agent in the Sanford Guide.

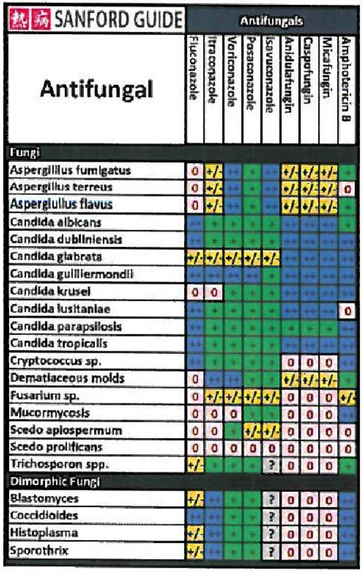
Active (+)
Agent is a potential alternative agent (active in vitro, possesses class activity comparable to known effective agents or a therapeutically interchangeable agents and hence likely to be clinically effective, but second line due to overly broad spectrum, toxicity, limited clinical experience, or paucity of direct evidence of effectiveness).

Variable (±)
Variable activity such that the agent, although clinically effective in some settings or types of infections is not reliably effective in others, or should be used in combination with another agent, and/or its efficacy is limited by resistance which has been associated with treatment failure.

Not Recommended (0)
Agent is a poor alternative to other agents because resistance to likely to be present or occur, due to poor drug penetration to site of infection or an unfavorable toxicity profile, or limited or anecdotal clinical data to support effectiveness.

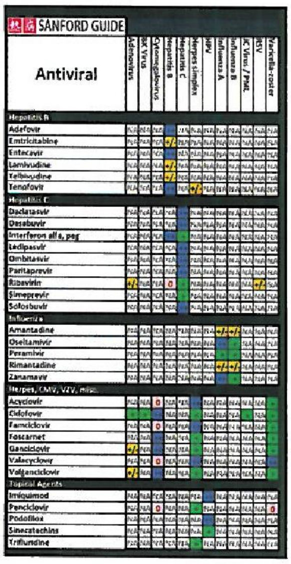
Insufficient Data (?)
Insufficient data to recommend use.

Not Applicable (NA)
Agent has no activity against this pathogen.



SANFORD GUIDE Antifungal

Antifungal	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Anidulafungin	Caspofungin	Micafungin	Amphotericin B
Fungi									
Aspergillus fumigatus	0	+/-	++	+	++	+/-	+/-	+/-	+
Aspergillus terreus	0	+/-	++	+	++	+/-	+/-	+/-	0
Aspergillus flavus	0	+/-	++	+	++	+/-	+/-	+/-	+
Candida albicans	++	+	+	+	+	++	++	++	+
Candida dubliniensis	++	+	+	+	+	++	++	++	++
Candida glabrata	+/-	+/-	+/-	+/-	+/-	++	++	++	++
Candida guilliermondii	++	++	++	++	+	++	++	++	++
Candida krusei	0	0	+	+	+	++	++	++	++
Candida lusitaniae	++	+	+	+	+	++	++	++	0
Candida parapsilosis	++	+	+	+	+	+	+	+	++
Candida tropicalis	++	+	+	+	+	++	++	++	++
Cryptococcus sp.	++	+	+	+	+	0	0	0	++
Dematiaceous molds	0	++	++	+	+	+/-	+/-	+/-	+
Fusarium sp.	0	+/-	+/-	+/-	+/-	0	0	0	+/-
Mucormycosis	0	0	0	+	+	0	0	0	++
Scedo apiospermum	0	0	+	+/-	+/-	0	0	0	0
Scedo prolificans	0	0	0	0	0	0	0	0	0
Trichosporon spp.	+/-	+	+	+	?	0	0	0	+
Dimorphic Fungi									
Blastomyces	+/-	++	+	+	?	0	0	0	++
Coccidioides	++	++	+	+	?	0	0	0	++
Histoplasma	+/-	++	+	+	?	0	0	0	++
Sporothrix	+/-	++	+	+	?	0	0	0	++



SANFORD GUIDE Antiviral

Antiviral	Adenovirus	BK Virus	Cytomegalovirus	Hepatitis B	Hepatitis C	Herpes simplex	HPV	Influenza A	Influenza B	JC Virus / PML	RSV	Varicella-zoster
Hepatitis B												
Adefovir	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA	NA
Emtricitabine	NA	NA	NA	+/-	NA	NA	NA	NA	NA	NA	NA	NA
Entecavir	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA	NA
Lamivudine	NA	NA	NA	+/-	NA	NA	NA	NA	NA	NA	NA	NA
Telbivudine	NA	NA	NA	+/-	NA	NA	NA	NA	NA	NA	NA	NA
Tenofovir	NA	NA	NA	++	NA	+/-	NA	NA	NA	NA	NA	NA
Hepatitis C												
Daclatasvir	NA	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA
Dasabuvir	NA	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA
Interferon alfa, peg	NA	NA	NA	++	+	NA	NA	NA	NA	NA	NA	NA
Ledipasvir	NA	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA
Ombitasvir	NA	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA
Paritaprevir	NA	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA
Ribavirin	+/-	NA	NA	0	+	NA	NA	NA	NA	NA	+/-	NA
Simeprevir	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA	NA
Sofosbuvir	NA	NA	NA	NA	++	NA	NA	NA	NA	NA	NA	NA
Influenza												
Amantadine	NA	NA	NA	NA	NA	NA	NA	+/-	+/-	NA	NA	NA
Oseltamivir	NA	NA	NA	NA	NA	NA	NA	++	+	NA	NA	NA
Peramivir	NA	NA	NA	NA	NA	NA	NA	+	+	NA	NA	NA
Rimantadine	NA	NA	NA	NA	NA	NA	NA	+/-	+/-	NA	NA	NA
Zanamavir	NA	NA	NA	NA	NA	NA	NA	++	+	NA	NA	NA
Herpes, CMV, VZV, misc.												
Acyclovir	NA	NA	0	NA	NA	++	NA	NA	NA	NA	NA	+
Cidofovir	+	+	++	NA	NA	+	NA	NA	NA	+	NA	+
Famciclovir	NA	NA	0	NA	NA	++	NA	NA	NA	NA	NA	+
Foscarnet	NA	NA	++	NA	NA	+	NA	NA	NA	NA	NA	+
Ganciclovir	+/-	NA	++	NA	NA	+	NA	NA	NA	NA	NA	+
Valacyclovir	NA	NA	0	NA	NA	++	NA	NA	NA	NA	NA	++
Valganciclovir	+/-	NA	++	NA	NA	+	NA	NA	NA	NA	NA	+
Topical Agents												
Imiquimod	NA	NA	NA	NA	NA	NA	++	NA	NA	NA	NA	NA
Penciclovir	NA	NA	0	NA	NA	+	NA	NA	NA	NA	NA	0
Podofilox	NA	NA	NA	NA	NA	NA	++	NA	NA	NA	NA	NA
Sinecatechins	NA	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA
Trifluridine	NA	NA	NA	NA	NA	+	NA	NA	NA	NA	NA	NA

Reference; Sanford® Guide to Antimicrobial Therapy
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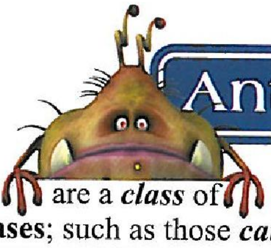
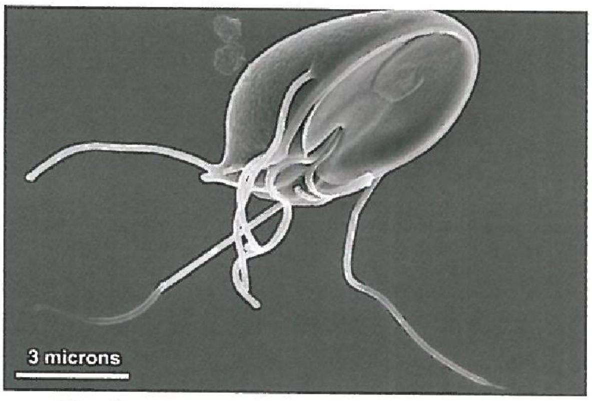
Pharmacy Dept. (content update - March 13, 2017)



Antiparasitic Drugs

- **Antiparasitics** are a *class* of **antimicrobial drugs** which are ***indicated for*** the **treatment** of **parasitic diseases**; such as those ***caused by*** **protozoa**, **helminths** and ***others***.
  - **Antiprotozoal Drugs** are **used** *to* **treat** ***protozoal infections***; which ***include*** **Amebiasis, Giardiasis, Cryptosporidiosis, Malaria, Trypanosomiasis, Leishmaniasis, Toxoplasmosis** and ***others***.
  - **Anthelmintic Drugs**; are **used** *to* **expel** **parasitic worms** (**helminths**) which ***include*** **Flatworms, Cestodes (Tapeworms), Trematodes (Flukes)** and **Nematodes (Roundworms)** and ***other*** **internal parasites** *from the* **body**.

Antiprotozoal Drugs



Giardia muris, a flagellate protozoan, is an intestinal parasite

- **Protozoa** are ***unicellular*** **eukaryotic organisms**.
- **Protozoa infections** ***range from*** **asymptomatic** *to* **life threatening** (in immunosuppressed patients, particularly patients with AIDS) ***depending on*** the ***species*** and ***strain*** of the **parasite** and the ***resistance*** of the **host**.
- **Protozoal infections** are ***common*** among **people** in ***underdeveloped*** **tropical** and ***subtropical*** **countries**, where **sanitary conditions**, **hygienic practices**, and ***inadequate control*** of the **vectors transmission**.
- ***Life Cycle***; - **Trophozoites**; are ***stages*** of **protozoa** that ***actively*** **feed** and **multiply**.
  - **Cysts**; are ***stages*** with a **protective membrane** or **thickened wall** *to* **survive** ***outside*** the **host**.
- ***Classification*** of **protozoa** ***according to*** **modes of transmission**;
  - **Enteric transmission**; ***Balantidium***, ***Giardia***, ***Entamoeba***, ***Cryptosporidium***, ***Toxoplasma***, ***Cyclospora***, **Microsporidia**.
  - **Sexual transmission**; ***Trichomonas***.
  - **Arthropod transmission**; ***Babesia***, ***Plasmodium***, ***Leishmania***, ***Trypanosoma***.
  - ***Other modes*** of **transmission**; ***Naegleria***, ***Acanthamoeba***, ***Toxoplasma***.
- ***Common*** **Protozoal Infections**;

Name	Disease	Transmission	Symptoms/Pathogen
Leishmania	Leishmaniasis	Sand-flies	**Visceral**; Fever, anemia & enlarged spleen & liver **Mucocutaneous/Cutaneous**; Ulcers
Trypanosoma brucei	**African Sleeping sickness (African trypanosomiasis)**	Tsetse fly	**African sleeping sickness**
Trypanosoma cruzi	**American trypanosomiasis**	Triatominae (Kissing bugs)	**Chagas disease**
Plasmodium	**Malaria**	Anopheles mosquito	**Vomiting, fever, headache, anemia** and **enlarged spleen** and **liver**
Giardia lamblia	**Giardiasis** (**beaver fever**)	Water/fecal-oral	**Diarrhea, abdominal pain** and **weight loss**
Trichomonas vaginalis	**Trichomoniasis**	Sexually	*Women*; **Vaginitis and thin yellowish/greenish fishy smell vaginal discharge** *Men*; **Burning** in the **penis** and **urethra** (**urethritis**)
Entamoeba histolytica	**Amoebiasis**	Water/fecal-oral	**Colitis, diarrhea, dysentery** and **liver abscess**
Cryptosporidium	**Cryptosporidiosis**	Water/fecal-oral	**Watery diarrhea** *with* or *without* **cough**
Toxoplasma gondii	**Toxoplasmosis**	- Eating poorly cooked food that contains cysts or exposure to infected cat feces. - From a mother to a child during pregnancy (if infected).	

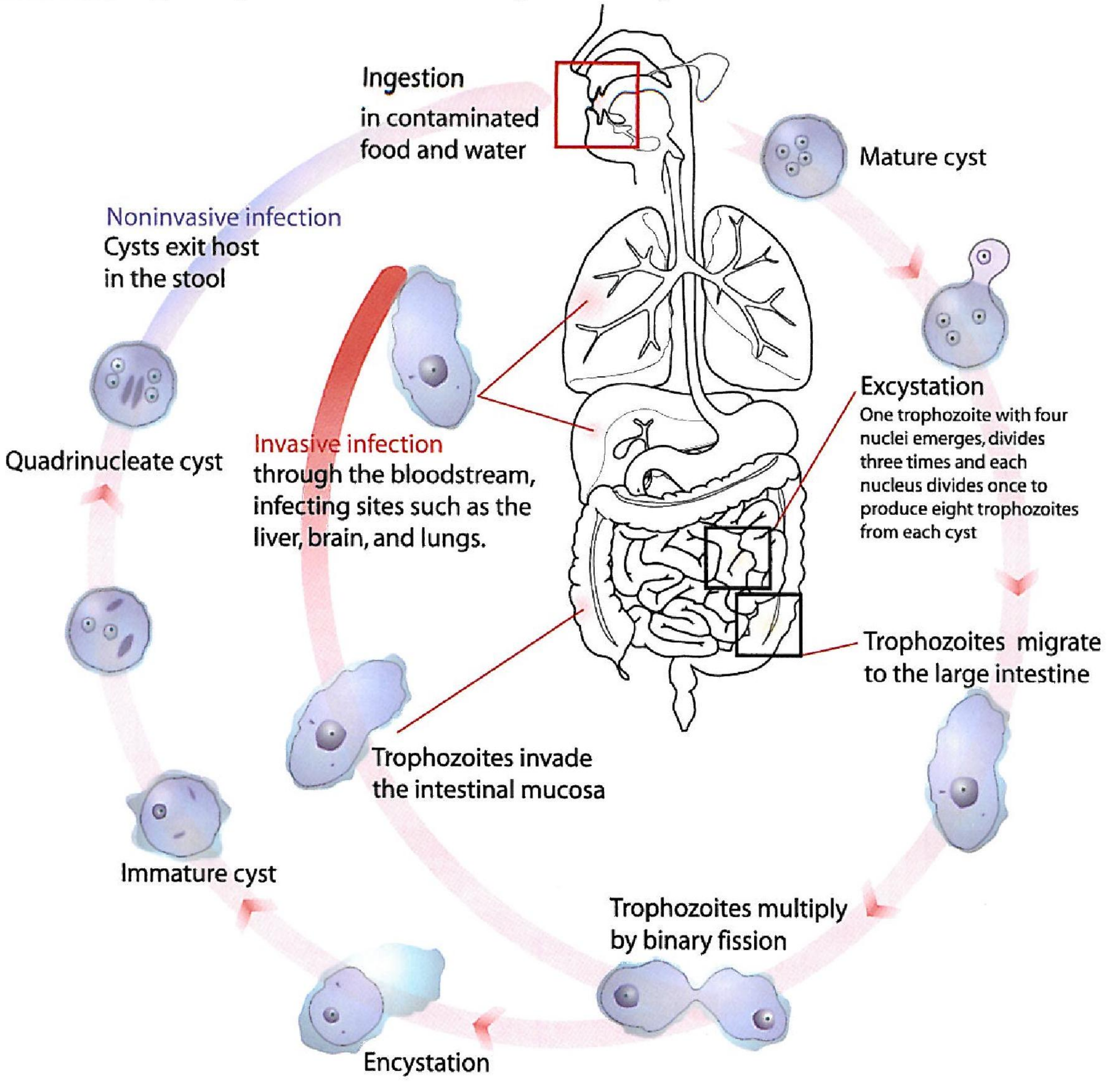
Dientamoeba, *Isospora* ,*Balantidium*, *Cyclospora* and **Microsporidia** (**Water/fecal-oral**); **Diarrhea**

Naegleria; *Primary* **amoebic meningoencephalitis** (**PAM**).

Acanthamoeba; **Keratitis** and **granulomatous amoebic encephalitis** (**GAE**).

Chemotherapy for Amoebiasis (Amebicides)

- **Amoebiasis (Amoebic Dysentery)** is an **infection** *caused by* ***any*** of the **amoebas** of the **Entamoeba group**, *commonly by* ***Entamoeba histolytica***.
- **Amoebiasis** can be **acute** or **chronic**, with *varying degrees* of **illness**, ***from*** **asymptomatic** *to* ***mild*** **diarrhea** *to* **dysentery** (**diarrhea** ***with*** **blood**).
- ***Entamoeba histolytica*** can *spread through the* **body**, ***most frequently*** **ending up** in the **liver** where it ***can cause*** **amoebic liver abscesses**.
- ***Diagnosis*** is typical by **stool examination** ***using*** a **microscope**.


Ingestion
in contaminated food and water
Mature cyst
Noninvasive infection
Cysts exit host in the stool
Excystation
One trophozoite with four nuclei emerges, divides three times and each nucleus divides once to produce eight trophozoites from each cyst
Quadrinucleate cyst
Invasive infection
through the bloodstream, infecting sites such as the liver, brain, and lungs.
Trophozoites migrate to the large intestine
Trophozoites invade the intestinal mucosa
Immature cyst
Trophozoites multiply by binary fission
Encystation

Life-cycle of *Entamoeba histolytica*

* Cysts and Trophozoites are passed in feces.

* Cysts are typically found in formed stool, whereas Trophozoites are typically found in diarrheal stool.

* Infection by *Entamoeba histolytica* occurs by ingestion of mature cysts in fecally contaminated food, water, or hands.

* Excystation occurs in the small intestine and Trophozoites are released, which migrate to the large intestine.

* The Trophozoites multiply by binary fission and produce cysts, and both stages are passed in the feces

* Cysts can survive days to weeks in the external environment and are responsible for transmission (protected by their walls) Trophozoites passed in the stool are rapidly destroyed once outside the body.

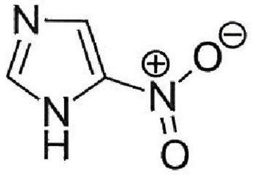
* In some patients the Trophozoites invade the intestinal mucosa, or, through the bloodstream, extra-intestinal sites such as the liver, brain, and lungs, with resultant pathologic manifestations.

- *Therapeutic agents* for **Amoebiasis** are *classified as*;
  - A) **Luminal amebicides**; are *effective against* **amebas** in the **lumen** of the **bowel** such as; **Iodoquinol**, **Paromomycin** and **Diloxanide Furoate**.
  - B) **Systemic amebicides**; are *effective against* **amebas** in the **intestinal wall** and **liver** such as; **Chloroquine** and **Dehydroemetine**.
  - C) **Mixed amebicides**; are *effective against* **both** the **luminal** and **systemic** *forms* such as; **Metronidazole** and **Tinidazole**, **Secnidazole** and **Ornidazole**.

Mixed Amebicides

Metronidazole (Flagyl®)

- **Metronidazole** [me-troe-NYE-da-zole] is a ***nitroimidazole***, is the ***mixed*** **amebicide** ***of choice*** for ***treating*** **amebic infections** (***kills*** **Trophozoites** but ***not*** **Cysts**) (***invasive*** **intestinal** or **extra-intestinal**)
- **Metronidazole** is also used in the ***treatment of***;
  - **Giardiasis** (***Giardia lamblia***) and **Trichomoniasis** (***Trichomonas vaginalis***).
  - **Infections** ***caused by*** ***anaerobic*** **cocci**, and ***anaerobic*** **gram-negative bacilli**.
  - ***Helicobacter pylori***-associated **peptic ulcer disease**.
  - ***Drug of choice*** for the *treatment of* **bacterial vaginosis**.
  - ***Drug of choice*** for the *treatment of* **pseudomembranous colitis** caused by ***Clostridium difficile***.
- **5-Nitroimidazoles** *include* **Metronidazole**, **Tinidazole** and **Secnidazole** used to ***combat*** ***anaerobic*** **bacterial** and **protozoal** ***infections***.



5-Nitroimidazole

- ***Mechanism of action***; ***Inhibits*** **nucleic acid synthesis** by ***disrupting*** **DNA** and ***causing*** **strand** ***breakage***; **amebicidal**, **bactericidal** and **trichomonacidal**;
  - The **nitro** ***group*** of **5-Nitroimidazole** is able to ***serve*** as an **electron acceptor**, and ***chemically*** **reduced** in **anaerobic bacteria** (*only in anaerobic cells*) and ***sensitive*** **protozoa**, *forming* ***reduced*** **cytotoxic compounds** that ***bind to*** **proteins** and **DNA**, ***resulting*** in **death** of **anaerobic bacteria** and **Trophozoites**.
- ***Pharmacokinetics***;
  - ***Absorption***; ***Completely*** and ***rapidly*** **absorbed** after **oral administration**.
  - ***Distribution***; ***Widely*** **distributed** *throughout* **body tissues** and **fluids** (vaginal and seminal fluids, saliva, breast milk and CSF).
  - ***Metabolism***; by the **liver**; **oxidation** (**CYP2C9**) *followed by* **glucuronidation**.
  - ***Excretion***; **Metronidazole** and its **metabolites** are **excreted** ***mainly*** in the **urine**.
- ***Dose*** for **Amebiasis**; - ***Adult***; 500-750 mg orally every 8 hours for 5-10 days.
  - ***Children***; 35-50 mg/kg/day orally/IV divided every 8 hours for 10 days.
- ***N.B.***; To ***kill*** **cysts** ***confined*** to the **intestine**; **Iodoquinol**, **Paromomycin** and **Diloxanide**; **One** of ***these drugs*** may **use** ***along with*** **Metronidazole**; **Furazol®**; **Metronidazole** + **Diloxanide**.

Side Effects

- ***Unpleasant*** **metallic taste**.
- **Nausea**, **vomiting** and **abdominal pain**.
- **Disulfiram-*like reaction***; Occur when **Metronidazole** ***ingested with*** **Alcohol** cause ***severe*** **flushing**, **tachycardia** and **hypotension** (**Disulfiram-*like reaction***).
- **Metronidazole** ***alone*** ***rarely*** *causes* **Stevens–Johnson syndrome**, ***but*** is reported to occur at ***high rates*** when ***combined with*** **Mebendazole**.
- ***Infrequent*** **side effects**; **diarrhea**, **insomnia**, **weakness**, **dizziness**, **thrush**, **rash**, **dysuria**, **dark urine**, **vertigo**, **paresthesia** and **neutropenia**.

- ***Pregnancy***; **FDA Category B** (No evidence of harm to the **fetus** *due to* **Metronidazole**).
- ***Lactation***; ***excreted in*** **human milk**; ***Not*** **recommended** (**Concentration** in the **milk** ***similar to*** **maternal serum** ***levels***).

- ***Warning***; **Metronidazole** *has been shown* to be **carcinogenic** in **mice** and **rats**.

Tinidazole (Fasigyn®) | Secnidazole (Flagentyl®) | Ornidazole (Ornidaz®)

- **Tinidazole**, **Secnidazole** and **Ornidazole** are ***nitroimidazole***, ***similar to*** **Metronidazole** in **spectrum** of **activity**, **absorption**, **adverse effects**, and **drug interactions**.
- ***Dose***; - **Tinidazole** (**Amebiasis**); 2 g (4 tab. 500 mg) orally once with food for 3 days (intestinal), 3-5 days (liver)
  - **Secnidazole** (**Bacterial Vaginosis**); 2 g (4 tab. 500 mg) orally once.

Luminal Amebicides

Iodoquinol (Yodoxin®)

- **Iodoquinol** [eye-oh-doe-KWIN-ole] or **Diiodohydroxyquinoline** is ***poorly*** **absorbed** from **GIT** and is used as a **luminal amebicide**.
- It is **effective** ***against*** the ***luminal*** **trophozoite** and **cyst** ***forms*** (*but* ***not*** **against trophozoites** in the **intestinal wall** or **extraintestinal tissues**); ***mechanism of action*** is **unknown**.
- **Iodoquinol** is **commonly** ***used with*** **Metronidazole** to *treat* **amebic infections**.
- ***Dose***; **Asymptomatic Amebiasis**; - ***Adult***; 650 mg 3 times daily for 20 days.
  - ***Children***; 30–40 mg/kg/d (max.: 2 g daily) in 3 divided doses for 20 days.
- ***Side effects***; **Rash**, **diarrhea** and **rarely** ***dose-related*** **peripheral neuropathy** (long-term use should be avoided).

Paromomycin (Humatin®)

- **Paromomycin** [par-oh-moe-MYE-sin], an ***aminoglycoside antibiotic***, ***poorly*** **absorbed** from **GIT** and **used** ***only*** as a **luminal amebicide** and has ***no*** **effect** ***against*** **extraintestinal amebic infections**.
- **Paromomycin** also **used** in **hepatic coma**, **cryptosporidiosis**, **giardiasis**, **leishmaniasis** and **tapeworm infection**.
- ***Dose***; **Luminal Amebiasis**; 25-35 mg/kg/day orally divided every 6 hours for 5-10 days.
- ***Side effects***; **Abdominal distress** and **diarrhea**.

Diloxanide Furoate (Amoebyl®)

- **Diloxanide Furoate** [dye-LOKS-ah-nide FYOOR-oh-ate] is a ***prodrug***, *metabolized* in the **GIT** *into* **Diloxanide**, used as a **luminal amebicide**.
- **Diloxanide Furoate** is **commonly** ***used with*** **Metronidazole** to *treat* **amebic infections** (**Furazol®**).
- ***Dose***; **Asymptomatic Amebiasis**; - ***Adult***; 500 mg 3 times a day for 10 days.
  - ***Children*** (>12 years); 20 mg/kg/d in 3 divided doses for 10 days.
- ***Most common side effect***; **Flatulence**.

Systemic Amebicides

Chloroquine

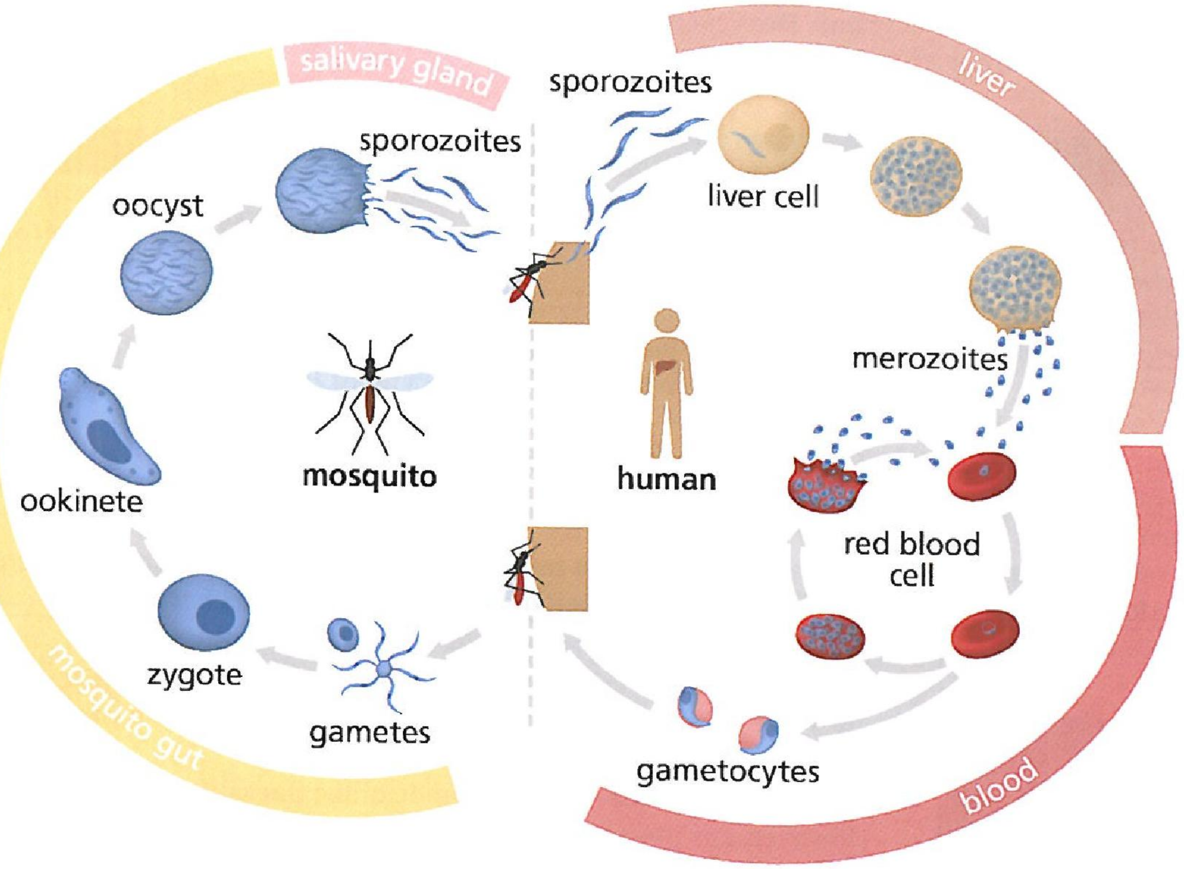
- **Chloroquine** [KLOR-oh-kwin] is an ***antimalarial drug***, also **used** in ***combination*** with **Metronidazole** (or ***other*** **nitroimidazole**) to ***treat*** **amebic liver abscesses**, in the ***case of*** **intolerance**, *but* it is ***not*** **useful** in ***treating*** **luminal amebiasis**. **Therapy** ***should be*** *followed with* a **luminal amebicide**.

Dehydroemetine

- **Dehydroemetine** [de-hye-dro-EM-e-teen] is an ***antiprotozoal drug*** ***similar to*** **Emetine** in its **anti-amoebic** ***properties*** and ***structure***, with ***fewer*** **side effects**.
- **Dehydroemetine** also **used** in **Leishmaniasis**.
- **Emetine** is an ***anti-protozoal drug*** and to ***induce*** **vomiting**. It is produced from the **ipecac root**. It takes its name from its **emetic** ***properties***.
- It is **used** *for* the ***treatment*** of **Metronidazole-*resistant*** **amoebiasis**.
- ***Administration*** by **IM injection** (**irritant** when ***taken*** **orally**; **Ipecac alkaloid**).
- ***Side effects***; **Pain** at the **site** *of* **injection**, **nausea**, **cardiotoxicity**, **neuromuscular weakness**, **dizziness** and **rash**.

Chemotherapy for Malaria (Antimalarial Drugs)

- **Malaria** is a ***mosquito-borne acute*** **infectious disease** *caused by* **4 species** of the **protozoal** ***genus Plasmodium***.
- The **disease** is *most commonly* ***transmitted by*** an ***infected*** **female** *Anopheles* **mosquito**.
- **Symptoms** that **typically** *include* **fever**, **tiredness**, **vomiting** and **headaches**; ***usually*** **begin 10-15 days** ***after*** **being** ***bitten***.
- ***Most*** **deaths** are ***caused by Plasmodium falciparum*** *because* ***Plasmodium vivax***, ***Plasmodium ovale***, and ***Plasmodium malariae generally*** cause a **milder** *form of* **malaria**.
- ***Plasmodium falciparum*** (**most dangerous**) ***may*** **cause**; ***persistent*** **high fever**, ***orthostatic*** **hypotension**, and ***massive*** **erythrocytosis** (abnormal elevation in the number of red blood cells accompanied by swollen, reddish limbs). ***Plasmodium falciparum*** **infection** *can lead to* **capillary** ***obstruction*** and **death** ***without*** **prompt treatment**.
- **Resistance** ***acquired*** by the **mosquito** to ***insecticides***, and by the **parasite** to ***drugs***, has ***led to*** **new therapeutic challenges**, ***particularly*** in the **treatment** of ***Plasmodium falciparum***.



Human malaria parasite life cycle

* A female *Anopheles* mosquito (definitive host) transmits a Sporozoite (motile infective form) to a vertebrate host such as a human (secondary host), thus acting as a transmission vector.

* A Sporozoite travels through the blood vessels to liver cells (hepatocytes), where it reproduces asexually (tissue schizogony), producing thousands of Merozoites.

* Merozoites infect new red blood cells and initiate a series of asexual multiplication cycles (blood schizogony) that produce 8 to 24 new infective Merozoites, at which point the cells burst and the infective cycle begins anew.

* Other Merozoites develop into immature gametocytes, which are the precursors of male and female gametes.

* When a fertilized mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut.

* The male and female gametocytes fuse and form an ookinete—a fertilized, motile zygote.

* Ookinetes develop into new Sporozoite that migrate to the insect's salivary glands, ready to infect a new vertebrate host.

- *Classification* of **Antimalarial drugs** *according to* **antimalarial activity**;
  - **Tissue Schizonticides**; These drugs *act on* **liver** *forms*, such as **Pyrimethamine** and **Primaquine**.
  - **Blood Schizonticides**; These drugs *act on* **blood** *forms*, such as **Chloroquine**, **Quinine**, **Mefloquine**, **Halofantrine**, **Pyrimethamine**, **Sulfadoxine**, **Sulphones**, **Tetracyclines** *etc.*
  - **Gametocides**; These drugs *kill* **sexual forms** and *prevent* **transmission** to **mosquitoes**, such as **Chloroquine** and **Quinine** (but *not* against *Plasmodium falciparum*).
  - **Sporontocides**; These drugs *prevent* the *development* of **oocysts** in the **mosquito**, such as **Primaquine** and **Chloroguanide**.
- *Classification* of **Antimalarial drugs** *according to* **the structure**;
  - **4-aminoquinolines**; **Chloroquine**, **Amodiaquine**.
  - **8-aminoquinolines**; **Primaquine**.
  - **Arylamino Alcohols**; **Quinine**, **Quinidine** (*Cinchona alkaloids*), **Mefloquine** and **Halofantrine**.
  - **Artemisinin Derivatives**; **Artemisinin** (**Qinghaosu** [ching-how-soo]) *derivatives* and *analogues* (Artemether, Arteether, Artesunate and Artelinic acid).
  - **Folate Synthesis Inhibitors**; **Pyrimethamine/Sulfadoxine** and **Proguanil**
  - **Naphthoquinones**; **Atovaquone**.
  - **Antibiotics**; **Tetracycline**, **Doxycycline**, **Clindamycin**, **Azithromycin** and **Fluoroquinolones**.
  - **Iron Chelating Agents**; **Desferrioxamine**.

4-aminoquinolines

Chloroquine (CQ) (Aralen®)

- **Chloroquine** [KLOR-oh-kwin] is a *synthetic* **4-aminoquinoline** that has been the *drug of choice* for *both* **treatment** and **chemoprophylaxis** of **malaria** *since the* **1940s** (**EXCEPT** in *resistant strains* of *Plasmodium falciparum*).
- **Chloroquine** also *effective* in the **treatment** of *extraintestinal* **amebiasis**.
- *Antimalarial Action*; - *Highly effective* **blood schizonticide**.
  - *Moderately* **effective** *against* **gametocytes** of *P. vivax*, *P. ovale* and *P. malariae* (*not against P. falciparum*).
  - **Not active** *against* **liver stage parasites**.
- *Resistance*; **Resistance** to **Chloroquine** is **now** *very common among* **strains** of *P. falciparum* and **uncommon** *but increasing* for *P. vivax*;
  - ***Resistance*** to **chloroquine** in *P. falciparum* can result from ***decreased*** **accumulation** of the **drug** in the **food vacuole** caused by the ***activity*** of a **transporter system** encoded by the ***pfcrt*** **gene**.

Mechanism OF Action

- *Mechanism of action* is *not fully* **understood**.
- *Inside* **red blood cells** (**erythrocytes**), the **malarial parasite**, *digests* the **host cell's hemoglobin** to *obtain essential* **amino acids** to *construct* its **own protein** and for **energy** *metabolism*.
- **Digestion** is *carried out* in a **vacuole** of the **parasitic cell**.
- However, this process also *releases* **large amounts** of *soluble* **heme**, which is *toxic* to the **parasite**. *To protect* **itself**, the **parasite** *polymerizes* the **heme** to **hemozoin** (a pigment), which is *sequestered* in the **food vacuole**.
- **Chloroquine** *binds* to **heme**, *preventing* its **polymerization** *to* **hemozoin**.
- The *increased* **pH** and the *accumulation* of **heme** result in *oxidative* **damage** to the **phospholipid membranes**, *leading to* **lysis** of *both* the **parasite** and the **red blood cell**.

Pharmaco Kinetics

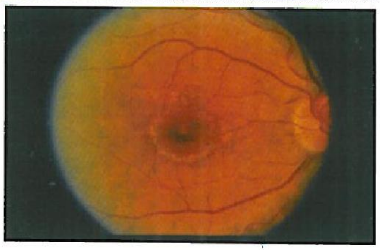
- *Absorption*; *Rapidly* and *completely after* **oral administration**.
- *Distribution*; *Very large* **volume of distribution** and *concentrates* in **erythrocytes**, **liver**, **spleen**, **kidney**, **lung** and *other* **cells** and **tissues** and *crosses* **placenta** and *enters* **breast milk**.
- *Metabolism*; *Dealkylated* in the **liver**.
- *Elimination*; **Urine** (~70% unchanged); *acidification* of **urine** ↑ **elimination**.

Prophylaxis should start 1 to 2 weeks before travel to malarious areas;
should continue weekly (same day each week) while in malarious areas and for 4 weeks after leaving such areas

Dose

- ***Adult dose*** for **malaria**;
  - ***Prophylaxis***; 500 mg Chloroquine phosphate (300 mg base) orally once/week
  - ***Treatment*** of **non-chloroquine-resistant**; 1 g Chloroquine phosphate (600 mg base) orally, THEN 500 mg Chloroquine phosphate (300 mg base) orally 6-8 hours later, THEN 500 mg Chloroquine phosphate (300 mg base) orally at 24 hours & 48 hours after initial dose.
- ***Child dose*** for **malaria** (< 60 kg);
  - ***Prophylaxis***; 8.3 mg Chloroquine phosphate/kg (5 mg base/kg) orally once/week.
  - ***Treatment*** of **non-chloroquine-resistant**; 1st dose: 16.7 mg Chloroquine phosphate/kg (10 mg base/kg) orally THEN 6 hours after 1st dose: 8.3 mg Chloroquine phosphate/kg (5 mg base/kg) orally repeated 24 hours after 1st dose and 36 hours after 1st dose.

Side Effects



- **GI upset**, **pruritus** and **headaches**.
- **Blurred vision** (**Chloroquine retinopathy**);
  - **Ophthalmologic examination *should be routinely* performed.**
- **QT interval prolongation** *may occur*.
- **Dosing *after* meals *may reduce some* side effects.**
- **Chloroquine** *may be associated* **hemolytic anemia** in **patients** *with* **glucose-6-phosphate dehydrogenase *deficiency*.**

Hydroxychloroquine (HCQ) (Plaquenil®)

- **Hydroxychloroquine** [hye-drox-ee-KLOR-oh-kwin] has *similar* **pharmacokinetics** to **Chloroquine**, with ***rapid* GI absorption, used for** the *prevention* and *treatment* of **malaria**.
- *Other uses*; **Rheumatoid arthritis** and **Systemic Lupus Erythematosus**.
- *Usual Adult Dose*;
  - **Malaria *Prophylaxis***; 400 mg (310 mg base) orally on the same day every week.
  - **Malaria *Treatment***; 800 mg (620 mg base) orally followed in 6 to 8 hours by 400 mg (310 mg base), then 400 mg (310 mg base) once a day for 2 consecutive days; alternatively, a single dose of 800 mg (620 mg base) has also been effective.

Amodiaquine (ADQ)

- **Amodiaquine** [AM-oh-dye-a-kwin] is a **4-aminoquinolone** *similar* in **structure** and **mechanism of action** to **Chloroquine**.
- **Amodiaquine** has been ***widely* used** in **Africa** to treat **malaria** *because* of its *low* **cost**, *limited* **toxicity** (*less* **itching**), and, in ***some* areas**, ***effectiveness against*** **Chloroquine-*resistant*** **strains** of ***Plasmodium falciparum***.
- **Amodiaquine** has ***become*** an **important drug** in the ***combination therapy*** for **malaria *treatment*** in **Africa**; ***first-line therapy*** for the *treatment* of ***uncomplicated*** **falciparum malaria** in ***many*** **countries** in **Africa**.
- The **World Health Organization (WHO)** *lists* **Amodiaquine** + **Artesunate** as a *recommended* therapy for **falciparum malaria** in ***areas*** with ***resistance*** to **older drugs**. This ***combination*** is **now *available*** as a **single tablet**; **ASAQ®**, **Arsucam®**, **Coarsucam®** and **Camoquin®**
- ***Another combination***, **Amodiaquine** + **Sulfadoxine-Pyrimethamine**, ***but*** is ***no longer*** **recommended**.

Piperaquine (PIP)

- **Piperaquine** [pi-PER-a-kwin] is a ***bisquinoline*** that ***was* used *widely*** to **treat Chloroquine-*resistant*** **strains** of ***Plasmodium falciparum*** in **China** in the **1970s** *through the* **1980s**, ***but*** its use waned *after* **resistance *became*** **widespread**.
- ***Recently***, **Piperaquine** has been ***combined with*** **Dihydroartemisinin** in ***co-formulated tablets*** (**Artekin®**, **Duo-cotecxin®**) that have ***shown excellent efficacy*** and ***safety*** for the ***treatment of*** **falciparum malaria**, ***without*** **apparent drug resistance** and was submitted for ***approval*** to the **European Medicines Agency** in **2009**.
- **Piperaquine-Dihydroartemisinin** is ***now*** the ***first-line therapy*** for the treatment of ***uncomplicated*** **malaria** in **Vietnam**; A change in the malaria treatment policy for Vietnam is in process now, due to study published in 2017 for treatment failure with **Piperaquine-Dihydroartemisinin**.

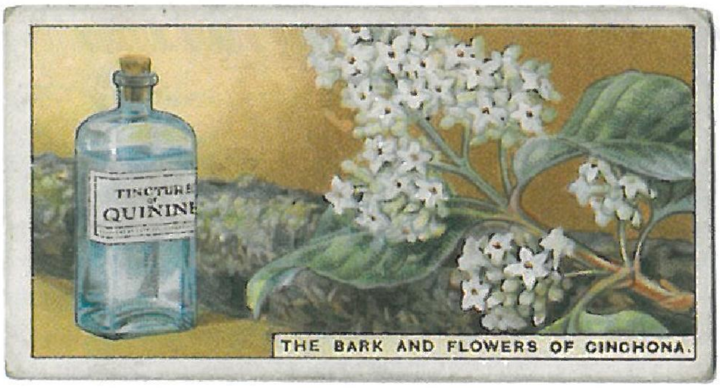
8-aminoquinolines

Primaquine

- **Primaquine** [PRIM a kween] is the *drug of choice* for the ***eradication*** of **dormant liver forms** of ***P. vivax*** and ***P. ovale*** and *can also* be **used** *in* **chemoprophylaxis** for ***all*** **malarial** *species*.
- **Primaquine** is *also* **used** to treat ***Pneumocystis*** **pneumonia**.
- *Mechanism of action*; **Primaquine** are **believed** to ***act as*** **oxidants** and cause ***oxidative damage*** to the **cell**; the ***exact mechanism*** is **not fully understood**.
- **All** ***Plasmodium*** **species** *may develop* **resistance** to **Primaquine**.
- *Pharmacokinetics*; ***Well*-absorbed orally**, *rapidly* **metabolized** by **liver** and *excreted* **renally**.
- *Usual Adult Dose*; ***for Uncomplicated P. vivax*** & ***P. ovale*** **malaria**; 30 mg orally once a day for 14 days (for *prophylaxis* used for 14 days after departure from malaria-endemic area)
- **Primaquine** is *associated with* ***drug-induced*** **hemolytic anemia** in ***patients with*** **glucose-6-phosphate dehydrogenase (G6PD) deficiency**; **Dose** in *mild* G6PD deficiency; 45 mg orally once a day for 8 weeks.
- *Large dose* may cause **abdominal discomfort** (*especially* when **used** in ***combination with*** **Chloroquine** and if taken on an ***empty*** **stomach**) and *occasional* **Methemoglobinemia**.

Arylamino Alcohols

- **Quinine** and *its isomer* **Quinidine** are ***extracted from*** the **bark** of the **Cinchona tree**; takes its name from the Inca language (South American Indians) for this substance (**quina-quina**; bark of barks).
- **Quinine alkaloid** was ***purified*** *from* the **bark** in **1820**, and it has been **used** in the ***treatment*** and ***prevention*** of **malaria** *since* that **time**.
- ***Even*** **today**, **Quinine** is ***obtained*** **entirely** from the **natural sources** *due* the **difficulties** in ***synthesizing*** the **complex molecule**.



THE BARK AND FLOWERS OF CINCHONA.

Quinine (QN) and Quinidine (QD)

- **Quinine** [KWYE-nine] and **Quinidine** [KWIH-nih-deen] ***remain*** **important therapies** for **falciparum malaria**; *especially* **severe disease**, ***although*** **toxicity** *may* **complicate** ***therapy***, *resistance* to **Quinine** is ***uncommon*** but ***may be increasing***.
- **Quinidine** is a ***dextrorotatory stereoisomer*** of **Quinine**, is at ***least*** as ***effective*** as ***parenteral*** **Quinine** in the treatment of ***severe*** **falciparum malaria** and has a ***shorter*** **half-life** *than* **Quinine**.
- **Quinidine** ***acts as*** a **class I antiarrhythmic agent** (**IA**) in the heart (↑ QRS complex and ↑ QT interval).
- **Quinine** ***absorption*** is ***reduced*** by **Aluminum-*containing*** **antacids**.
- *Mechanism of action*; ***Like*** **Chloroquine**, ***interferes*** with **heme** ***polymerization***, *resulting in* **death** of the **erythrocytic form** of the **plasmodial parasite**.
- *Antimalarial Action*; **Quinine** is a ***rapid-acting***, ***highly effective*** **blood schizonticide** ***against*** the **four species** of ***human*** **malaria parasites**. The drug is **Gametocidal** ***against P. vivax*** and ***P. ovale*** but ***not P. falciparum***. It is ***not active*** **against liver** ***stage*** **parasites**.
- *Resistance* to **Quinine** is ***already*** **common** in *some* **areas** of **Southeast Asia**, *especially* **border areas** of **Thailand**, where the **drug** ***may*** **fail** if **used** ***alone*** to treat **falciparum malaria**.
- **Quinine** is ***first-line*** **therapy**, in ***combination*** with **Clindamycin**, in the ***treatment of*** **infection** *with* ***Babesia microti*** or other ***human*** **babesial infections** (**Babesiosis**).
- **Quinine** is a ***flavor component*** of **tonic water**.
- *Usual Adult Dose*; 648 mg orally 3 times a day for 7 days (in ***combination with*** **Tetracycline**, **Doxycycline**, or **Clindamycin** in **Chloroquine-*Resistant P. falciparum***).

Side Effects

- **Cinchonism Syndrome**; **Tinnitus, headache, nausea, dizziness, flushing,** and **visual disturbances** (*reversible*); Not reasons for suspending therapy.
- **Hemolytic anemia** (*especially* in ***G6PD deficiency***), **Thrombocytopenia** & **Leukopenia**; **Quinine** therapy ***should be*** suspended.
- **Hypersensitivity reactions**; **rashes, angioedema & bronchospasm.**
- It ***must*** be **used** with ***great*** **caution** in **patients** with **cardiac abnormalities**.

Mefloquine (MQ) (Lariam®)

- **Mefloquine** [MEF-lo-kwin] was ***developed*** *during* **Vietnam War** and is ***chemically related*** to **Quinine**.
- **Mefloquine** is **one** of the ***recommended*** **chemoprophylactic drugs** for use in ***most*** **malaria-endemic regions** *with* **Chloroquine-*resistant* strains** (**Chloroquine- *resistant P. falciparum***).

Pharmaco Kinetics

- ***Only*** ***administrate*** **orally** (**severe local irritation** occurs *with* **parenteral use**).
- ***Well*** **absorbed**; ***bioavailability*** >85%; food **enhances** bioavailability ~40%.
- ***Long*** **half-life** (20 days) (enterohepatic *circulation*, *highly* protein-bound and ***extensively*** concentration in tissues); ***allowing*** **BEST** ***weekly*** **dosing** for **chemoprophylaxis**.
- ***Extensively*** **metabolized** in liver by **CYP3A4**.
- ***Mainly*** ***excreted*** in **bile** *into the* **feces**.

- ***Antimalarial*** ***action***; ***Strong*** **blood** **schizonticidal** activity ***against P. falciparum*** and ***P. vivax***, but it is ***not active*** ***against*** **hepatic stage (tissue)** or **gametocytes**.

Dose

- **Acute Malaria Infections**; **1250 mg orally *once* as a single dose.**
- **Malaria Prevention**; **250 mg orally *once* weekly** on the ***same* day** of ***each* week**; **1-2 *week* before >> during >>> 4 *weeks* after**
  - ***Start*** **1-2 weeks *before* arrival in endemic area.**
  - ***Continue*** *every* **week *during* staying in endemic area.**
  - ***Continue*** **4 weeks *after* leaving endemic area.**

Side Effects

- ***Most common***; **nausea**, **vomiting** and **dizziness**.
- **FDA Warning**;
  * **Neuropsychiatric side effects**; **Depression**, **hallucinations** and **anxiety**.
  * **Neurological side effects**; ***Poor* balance**, **seizures** and **tinnitus**.
- **Mefloquine** *may cause* ***abnormalities*** with **heart rhythms**.

Halofantrine (Halfan®)

- **Halofantrine** [ha-loe-FAN-trin] is a **drug** ***used to*** **treat** **malaria**, it belongs to the ***phenanthrene class*** of **compounds** that *includes* **Quinine** and **Lumefantrine**.
- **Lumefantrine** (or **Benflumetol**) is an ***antimalarial drug***. It is ***only*** **used** in ***combination with*** **Artemether** (**Coartem®**).
- **Halofantrine** is ***never*** **used** to ***prevent*** **malaria** and its **mode of action** is ***unknown***.
- **Halofantrine** ***should be*** **taken** on an ***empty*** **stomach** (**bioavailability** and *risk of* **toxicity** ***increased with*** **fatty food**). ***Half-life***; *about* **4 days**.
- ***Common Side Effects***; - **Abdominal pain**, **diarrhea**, **vomiting**, **rash** and **headache**.
  - **Cardiotoxicity** (**QT *prolongation***); ***should not*** **be used** *with* **Mefloquine**.

Artemisinin Derivatives

- **Artemisinin** or **Qinghaosu** [ching-how-soo] is the ***active*** **principal** of the **Chinese medicinal herb** ***Artemisia annua*** الشيح. It has been used as **treatment** ***of*** **fevers** in **China** for ***more than*** **1000 years**.
- The **antimalarial value** of ***Artemisia annua*** was ***first*** **documented** in ***written*** *as early as* **340 AD**.
- The **active *antimalarial* constituent** of this **plant** was ***isolated*** in **1971** and it was *named* **Artemisinin** by **Tu Youyou** and the **drug** is ***named*** **Qinghaosu** [ching-how-soo] in Chinese.
- **Treatments *containing*** an **Artemisinin** and its ***derivatives*** (**Artemisinin-*combination* therapies, ACTs**) are ***now*** **standard treatment worldwide** for ***P. falciparum*** **malaria**.

- Tu Youyou (born 30 December 1930) is a Chinese pharmaceutical chemist and educator.
- She is best known for discovering Artemisinin (Qinghaosu [ching-how-soo]) and dihydroartemisinin, used to treat malaria, and which has saved millions of lives.
- Tu Youyou carried on her work in the 1960s.

* For her work, Tu received the 2011 Lasker Award in clinical medicine and the 2015 Nobel Prize in Physiology or Medicine.

Artemisinin or Qinghaosu

- **Artemisinin** [ar-te-MIS-in-in] ***its* derivatives** are ***recommended* first-line agents** for the *treatment of* ***multidrug-resistant P. falciparum*** **malaria**.
- The ***most important*** of these **derivatives** or **analogs** are;
    - **Artesunate (AS)**; **water-soluble**; useful for oral, IV, IM and rectal administration.
    - **Artemether (ART)**; **lipid-soluble**; useful for oral, IM and rectal administration.
    - **Dihydroartemisinin (DHA)**; **water-soluble**; useful for oral administration.
- To ***prevent*** the ***development of*** **resistance**, ***these*** **agents** ***should not*** be **used *alone***, **companion drugs** *include*; **Lumefantrine**, **Mefloquine**, **Amodiaquine**, **Sulfadoxine/Pyrimethamine**, **Piperaquine** and **Chloroproguanil/Dapsone.**
- ***Pharmacokinetics***;
    - **Artemisinin** and ***its* analogs** are ***rapidly*** **absorbed** (half-lives of 1–3 hours after oral administration).
    - **Artemisinin**, **Artesunate** and **Artemether** are ***rapidly*** **metabolized** to the ***active metabolite*** **Dihydroartemisinin**.
- ***Mechanism of action***; ***not completely*** **understood**;
    - May result from the production of free radicals that follows the iron-catalyzed cleavage of the Artemisinin endoperoxide bridge in the parasite food vacuole
    - New theory; may result from inhibition of a parasite sarcoplasmic-endoplasmic reticulum calcium ATPase.
- ***Antimalarial action***; ***Very rapidly*** *acting* **blood schizonticides *against all* human malaria parasites** (***fastest*** *acting* **anti-malarial *available***).
- ***Doses***;

	Injection	Oral
Artemether	3.2 mg/kg IM as a loading dose; Followed by 1.6 mg/kg daily until oral therapy	4mg/kg on first day; Followed by 2mg/kg
Artesunate	2.4 mg/kg followed by 2.4mg/kg after 12 hours, 24 hours and once daily thereafter	4 mg/kg
Arteether (Artemotil)	3 mg/kg once a day for 3 days, as deep IM	-
Dihydroartemisinin	-	120 mg initially, then 60 mg daily for a further 4 to 6 days

- ***Currently*** **Artemisinin-*based combination therapy* (ACT)** and ***recommendations***;

  R; WHO Guidelines for the treatment of malaria. 3rd edition, April 2015

    - *For* ***uncomplicated*** **falciparum malaria** (Adult and children, EXCEPT pregnant in 1st trimester);

      ACT regimens *should* provide 3 days' treatment with an Artemisinin derivative

        - **Artemether** + **Lumefantrine** (Coartem®)
        - **Artesunate** + **Amodiaquine** (Camoquin®)
        - **Artesunate** + **Mefloquine** (Artequin®)
        - **Artesunate** + **Sulfadoxine/Pyrimethamine (SP)**
        - **Dihydroartemisinin** + **Piperaquine** (Duo-Cotecxin®)

        * **Pregnant** in **1st *trimester***; **Quinine** + **Clindamycin** *for* 7 days.

        * If the **malaria species** is ***not known*** with certainty, ***treat as*** for **uncomplicated *P. falciparum*** malaria.
    - *For* ***severe*** **malaria**;
        - **IV** or **IM Artesunate** for *at least* **24 hours** and ***until*** they *can tolerate* **oral medication, once a patient** has ***received at least*** **24 hours** of ***parenteral*** **therapy** and ***can*** **tolerate oral therapy, *complete*** **treatment** *with* **3 days** of **ACT**.

Side Effects

- **Artemisinins** are ***generally very well*** **tolerated**.
- ***Most commonly*** *reported*; **Nausea**, **vomiting**, **anorexia** and **dizziness**.
- ***High doses*** may cause **QT interval *prolongation***.
- **Hypersensitivity *reactions*** and **rash** *may* **occur**.
- **Neutropenia**, **anemia** and ***elevated*** **liver enzymes**, have been noted ***rarely***.
- ***Irreversible*** **neurotoxicity** has been seen in ***animals***.
- ***Pregnancy***; ***No*** **Artemisinins-*related*** **adverse pregnancy *outcomes*** have been ***reported***. However, there is ***insufficient*** **evidence** *regarding* the ***safety*** of **Artemisinins *use*** in the **first trimester** of ***pregnancy***.

Folate Synthesis Inhibitors and Others

Sulfadoxine/Pyrimethamine (Fansidar®)

- **Pyrimethamine** [peer-i-METH-a-meen] ***inhibits*** **dihydrofolate reductase** *required for* the ***synthesis*** of **Tetrahydrofolate** (a cofactor needed for synthesis of nucleic acids).
- **Sulfadoxine** [sul-fa-DOX-een] is an ***ultra-long-lasting*** **sulfonamide**.
- **Pyrimethamine/Sulfadoxine** are typically *given* with **Folinic acid** (**Leucovorin**; to reduce side effects related to folate deficiency in the patient).
- **Pyrimethamine/Sulfadoxine** **now** ***used*** in ***combination*** with **Artesunate** for the ***treatment*** of ***uncomplicated P. falciparum*** **malaria**.
- **Pyrimethamine** is also **used** in ***combination*** with **Sulfadiazine** to treat ***active*** **toxoplasmosis**.
- **Pyrimethamine** is also **used** *with* **Dapsone** as a ***second line*** option to **prevent** ***Pneumocystis jiroveci*** **pneumonia (PCP)** in **people** *with* **HIV/AIDS**.
- ***Doses***; - **Malaria** ***treatment***; 2-3 tablet orally once (**Pyrimethamine** 25mg/**Sulfadoxine** 500mg).
  - **Malaria** ***prophylaxis***; 1tab every week OR 2tab every 2week; **1-2*week*** **before** > **during** > **4*weeks*** **after**
- ***Common Side Effects***; - **GI upset**, **rash**, **headache**, **Photosensitivity** and **hair loss**.
  - **Agranulocytosis** and **aplastic anemia** *may occur*.

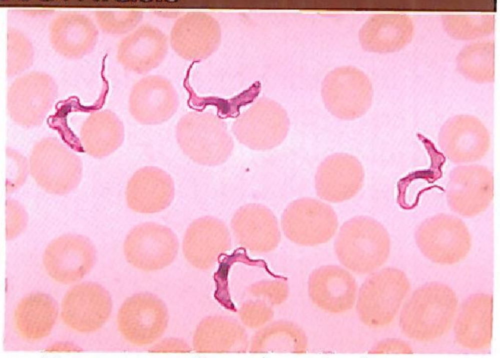
Chloroguanide (Proguanil)/Atovaquone (Malarone®)

- **Proguanil** (**Chloroguanide**) [pro-GWA-nil] is a ***biguanide derivative*** that is *converted to* an **active metabolite** called **Cycloguanil**, is an ***inhibitor*** of **dihydrofolate reductase**.
- **Atovaquone** [a-TOE-va-kwone] is a ***synthetic*** **hydroxynaphthoquinone**, ***inhibits*** **mitochondrial processes** *such as* **electron** ***transport***, as well as **ATP** and **pyrimidine** ***biosynthesis***.
- **Atovaquone/Proguanil** is ***fixed*** **dose** ***combination*** *approved for* **both** ***treatment*** and ***prophylaxis*** of **malaria** in **chloroquine-resistant areas**.
- It is *available as*; - **250 mg Atovaquone + 100 mg Proguanil** *per* **tablet** ***for*** **adults**.
  - **62.5 mg Atovaquone + 25 mg Proguanil** *per* **tablet** ***for*** **children**.
- ***Usual Adult Dose***; - ***Prophylaxis***; 1 tablet orally daily, beginning 1-2 days before travel to malaria-endemic area and continued until 7 days after return.
  - ***Treatment***; 4 tablets orally daily for 3 days.
  - * In ***event of*** **vomiting** *within* **1 hour** of **dose**, ***repeat*** **dose**.
  - * It ***should be*** **taken** *with* **food** or **milk** to ***enhance*** **absorption**.
- ***Common Side Effects***; **Nausea, vomiting, abdominal pain, headache** and ***increase*** **liver enzymes**.

Other Drugs with Antimalarial Activity

- **Tetracyclines**; - These drugs are ***useful*** in **treating** a ***broad range*** of **infections**, *including* **malaria**.
  - *Both* **Tetracycline** and **Doxycycline** are equally effective.
    - **Tetracycline**; 250 mg every 6 hours for 7-10 days.
    - **Doxycycline**; 100 mg twice daily for 7-10 days.
    - **Doxycycline** is also used for short term prophylaxis; 100mg once daily.
- **Clindamycin**; can be used for ***drug resistant*** **malaria** along with **Quinine** at a dose of **10 mg/kg 8** ***hourly*** for **5 days** and in **pregnant** in **1st** ***trimester*** with **Quinine** *for* 7 days.
- **Azithromycin** is **found** to *have* **anti-malarial** ***activity***.
- **Fluoroquinolones**; **Ciprofloxacin** & **Norfloxacin** have been **found** to *have* **anti-malarial** ***activity***.

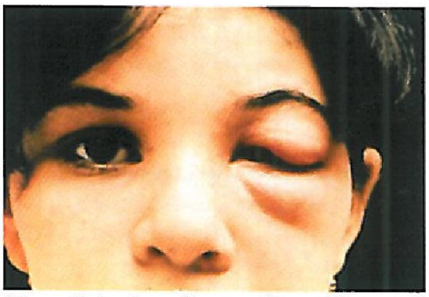
Chemotherapy for Trypanosomiasis



Trypanosoma forms in a blood smear

- **African trypanosomiasis** (**sleeping sickness**) and **American trypanosomiasis** (**Chagas disease**) are two ***chronic*** and, ***eventually***, **fatal diseases** caused by species of *Trypanosoma*.
- *In* African sleeping sickness;
  - *Causes*; *Trypanosoma brucei gambiense* (**TbG**) and *Trypanosoma brucei rhodesiense* (**TbR**). **TbG** causes **over 98%** of reported cases.
  - **Both** are usually ***transmitted by*** the **bite** of an ***infected* tsetse fly** and are ***most common*** in **rural areas**.
  - **Both** are *live* and ***grow*** in the **blood**.
  - The **parasite *later*** invades the **CNS**, *causing* **inflammation** of the **brain** and **spinal cord** that ***produces*** the characteristic **lethargy** and *eventually*, ***continuous* sleep**.

- *In* Chagas' disease;
  - *Causes*; *Trypanosoma cruzi*.
  - ***Transmitted by* insects** known as **Triatominae** (**kissing bugs**)
  - ***Acute* Chagas disease**; **fever** or **swelling *around*** the **site** of **inoculation**. ***Rarely***, **acute infection** may result in ***severe* inflammation** of the **heart muscle** or **brain**.
  - ***About* 20-30%** of ***infected* people** will *develop* **heart failure**, ***enlarged* esophagus** or an ***enlarged* colon**.



Romaña's sign, the swelling of the eyelid, is a marker of acute Chagas' disease

Pentamidine (Pentam®) (NebuPent®)

- **Pentamidine** [pen-TAM-i-deen] is ***active against*** a *variety of* **protozoal infections**, including; ***first stage*** of **African trypanosomiasis**, **Leishmaniasis**, **Babesiosis**, and to ***prevent*** and ***treat*** **pneumocystis pneumonia** (*caused by Pneumocystis jirovecii*); *Pneumocystis jirovecii* is an ***atypical* fungus** that causes **pneumonia** in **immunocompromised patients**, such as those with **HIV infection**. **Trimethoprim/Sulfamethoxazole** is ***preferred*** in the **treatment** of *P. jirovecii* infections; however, **Pentamidine** is an ***alternative*** in individuals who are ***allergic to*** **Sulfonamides**.
- *Pharmacokinetics*;
  - *Administration*; ***only*** **parenterally** (IM or IV); **Pentamidine** can also be ***inhaled*** as a **nebulized powder** (**NebuPent®**) for the ***prevention*** of **pneumocystosis**.
  - *Distribution*; **distributes *widely*** and is ***concentrated*** in the **liver**, **kidney**, **adrenals**, **spleen** and **lungs**; ***because*** it does ***not enter*** the **CSF**, it is **ineffective *against*** the ***second stage*** (**CNS involvement**) of **trypanosomiasis**.
  - *Metabolism* and *excretion*; ***not* metabolized**, and **excreted *very slowly*** in **urine**.
- *Mechanism of action*; Inhibits synthesis of DNA, RNA, phospholipids and protein.
- *Dose* for **Trypanosomiasis** in ***first stage*** (**hemolymphatic**); 4 mg/kg IM/IV once a day for 7 to 10 days
  - *First line* in **West African Trypanosomiasis**; *Trypanosoma brucei gambiense*.
  - *Second line* in **East African Trypanosomiasis**; *Trypanosoma brucei rhodesiense* (**Suramin** is a ***first line*** agent).

* ***Rapid* IV** *administration* can *lead to* ***severe* hypotension**, **tachycardia**, **dizziness** and **dyspnea**, so the drug ***should be* administered *slowly*** (*over* **2 hours**).

* **IM *administration***; **pain** at the ***injection site*** is **common**, and ***sterile* abscesses may develop**.

- *Common side effects*; **Leukopenia**, **nephrotoxicity** (***increased* serum creatinine** and **urea**), ***increased* liver enzymes**, **pancreatitis**, **hypoglycemia** or **hyperglycemia** and **bronchospasm** (*with* **inhalation**).

Suramin

- **Suramin** [SOO-ra-min] is a ***sulfated* naphthylamine used *primarily*** in the ***first stage*** (***without* CNS involvement**) of **East African Trypanosomiasis** (*Trypanosoma brucei rhodesiense*) as ***first line***.
- **Suramin** is *less* **effective *than* Pentamidine** for ***early* West African Trypanosomiasis**.
- *Mechanism of action*; **unknown**.
- *Dose*; 100-200 mg (test dose) IV ***only***, then 1 g IV on days 1, 3, 7, 14, 21.
- *Common side effects*; **Nausea** and **vomiting**, **urticaria**, **shock** and **neurologic *problems*** (paresthesia, photophobia, and hyperesthesia of the hands and feet) and **renal abnormalities**.

Melarsoprol (Arsobal®)

- **Melarsoprol** [mel-AR-so-prol], a ***trivalent*** **arsenical compound**, is **used** *for* the **treatment** of **African Trypanosomiasis** in the **second stage (CNS involvement)**;
    - ***First line*** and ***only*** **available** in **second stage** *of* **East African Trypanosomiasis**; ***Trypanosoma brucei rhodesiense.***
    - ***Second line*** in **second stage** *of* **West African Trypanosomiasis**; ***Trypanosoma brucei gambiense*** (**Eflornithine** is a ***first line*** **agent**).
- ***Mechanism of action***; **Melarsoprol** is a ***prodrug***, which is *metabolized to* **Melarsoprol oxide (Mel Ox)** as its **active *form***. **Mel Ox** is an **arsen-oxide** that ***irreversibly* binds** to **vicinal sulfhydryl** groups on **pyruvate kinase**, which ***disrupts* energy production** in the **parasite**. The ***inability*** **to distinguish *between* host** and **parasites** renders this drug ***highly* toxic** with ***many* side effects**.
- ***Dose***; - 2-3.6 mg/kg/day IV for 3 days.
    - After 1 week: 3.6 mg/kg/day IV for 3 days.
    - Repeat again after 10-21 days: 3.6 mg/kg/day.
- ***Common side effects***; **Encephalopathy**, **hypertension**, **myocardial damage** & **peripheral neuropathy**.
- ***Warning***; **Hemolytic anemia** in **patients** with **glucose-6-phosphate dehydrogenase (G6PD) *deficiency*** and **hypersensitivity reactions** *may* **occur**.

Eflornithine (Ornidyl®)

- **Eflornithine** [ee-FLOOR-nih-theen] (**Di-fluoro-methyl-ornithine**) is an ***irreversible*** of ***ornithine decarboxylase inhibitor***. ***Inhibition*** of ***this*** **enzyme *inhibit*** the **production** of **polyamines** in the **parasite**, thereby *leading to* **cessation** of **cell *division***.
- **Eflornithine** is a ***first-line*** for **second stage** *of* **West African Trypanosomiasis**; ***Trypanosoma brucei gambiense*** (**Melarsoprol** is a ***second line*** **agent**).
- ***Topical*** **Eflornithine** (**Vaniqa®**) is the ***first*** and ***only*** *approved* **cream** to ***reduce unwanted* facial hair** in **women**.
- ***Dose***; 400 mg/kg/day divided every 6 hours IV for 14 days, then 300 mg/kg/day orally for 3-4 weeks.
- ***Common side effects***; **Anemia**, **leukopenia**, **thrombocytopenia**, **seizures** (may be due to the disease) and ***temporary*** **hearing loss**.

Nifurtimox (Lampit®)

- **Nifurtimox** [nye-FER-tim-oks] is a ***nitrofuran***, is **used** as a ***second line*** (**Benznidazole** is a ***first line*** **agent**) for **American Trypanosomiasis (Chagas' disease)** and may use in ***combination*** with **Eflornithine** for **second-stage West African Trypanosomiasis**; ***Trypanosoma brucei gambiense***.
- ***Mechanism of action***; **Nifurtimox** ***forms*** a **nitro-anion radical *metabolite*** that ***reacts*** with **nucleic acids** of the **parasite** *causing* ***significant*** *break down* of **DNA**.
- ***Dose***; 8-10 mg/kg/day orally divided every 6-8hr for 90-120 days.
- ***Side effects***; **Anorexia** (50-60% can limit completion of therapy), **nausea**, **vomiting**, **abdominal pain**, **fever**, **rash**, **restlessness**, **insomnia**, **neuropathies** and **seizures**.

Benznidazole (Rochagan®)

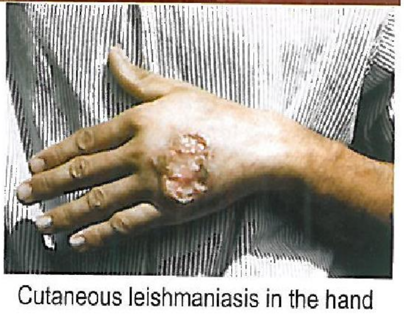
- **Benznidazole** [benz-NI-da-zole] is a ***nitroimidazole derivative*** with a ***mechanism of action*** *similar to* **Nifurtimox**.
- **Benznidazole** is used as a ***first line*** treatment of **Chagas disease**, it tends to be **better tolerated *than* Nifurtimox**.
- ***Dose***; 5-7 mg/kg/day orally divided in 2 doses separated by ~12 hours for 60 days.
- ***Common side effects***; **Abdominal pain**, **rash** and **peripheral neuropathy**.

Treatment of African Trypanosomiasis

	Stage	First-Line Drugs	Alternative Drugs
West African	Early	Pentamidine	Suramin, Eflornithine
	CNS involvement	Eflornithine	Melarsoprol, Eflornithine/Nifurtimox
East African	Early	Suramin	Pentamidine
	CNS involvement	Melarsoprol	

Chemotherapy for Leishmaniasis

- **Leishmaniasis** is a *disease caused by* **parasites** of the ***Leishmania*** **type**.
- It is ***spread by*** the **bite** of ***certain*** **types** of **sand-flies**.
- There are **3 types** of **Leishmaniasis**:
  - **Cutaneous leishmaniasis**; Skin ulcers.
  - **Mucocutaneous leishmaniasis**; Ulcers of skin, mouth and nose.
  - **Visceral leishmaniasis**; Skin ulcers and then later presents with fever, low red blood cells, and enlarged spleen and liver.



Cutaneous leishmaniasis in the hand

- ***Medications***;
  - ***Pentavalent*** **Antimonial Agents**; **Sodium Stibogluconate** & **Meglumine Antimoniate**.
  - ***Liposomal*** **Amphotericin B** (systemic antifungal).
  - ***Oral*** **Miltefosine**.
  - **Pentamidine** (anti-trypanosoma).
  - **Paromomycin** (Aminoglycoside; luminal amebicide).
  - **Fluconazole** (antifungal).
  - **Allopurinol** (Xanthine Oxidase Inhibitors).

Sodium Stibogluconate (Pentostam®)

Meglumine Antimoniate (Glucantim®)

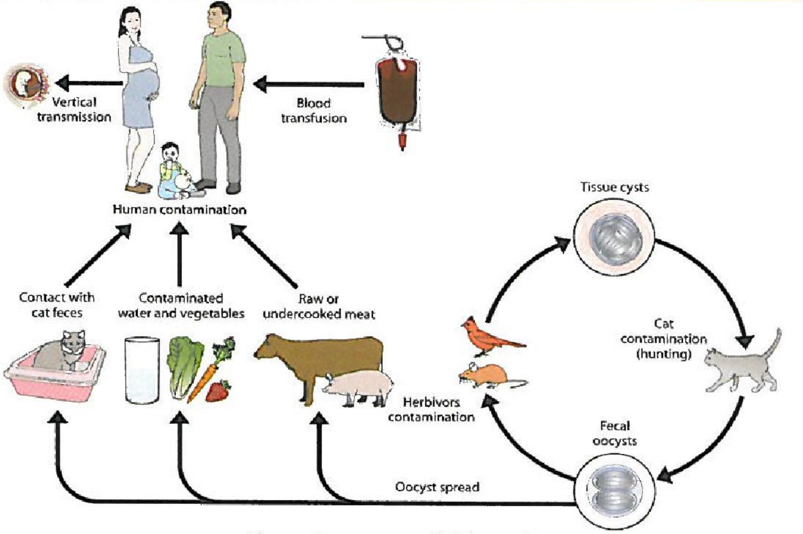
- **Sodium Stibogluconate** [stib-o-GLOO-koe-nate] and **Meglumine Antimoniate** [MEG-loo-meen anti-MOE-nee-ate] are ***Pentavalent*** **Antimonial Agents**.
- **Sodium Stibogluconate** is ***only*** **available** in **CDC treatment** ***protocols***.
- They are *generally* **considered** ***first-line*** **agents** for **cutaneous** and **visceral leishmaniasis** ***except*** in ***parts*** of **India** (**Amphotericin B** are **considered** ***first-line*** **agents**).
- ***Mechanism of action***; is ***poorly*** **understood**.
- They are ***not*** **absorbed** *after* **oral administration**, ***must*** be **administered** ***parenterally***.
- ***Dose***; **Sodium Stibogluconate**; 20 mg/kg/day (maximum 850 mg) IV/IM for 20-28 days.
- ***Common side effects***; **GI symptoms**, **fever**, **headache**, **myalgias**, **arthralgias**, **rash** and **QT prolongation**.
- **Renal** and **hepatic function** *should be* ***monitored*** **periodically**.

Miltefosine (Impavido®)

- **Miltefosine** [mil-te-FOE-zeen] is the ***first*** **orally active drug** for **visceral leishmaniasis**.
- It *may* also have ***some activity against*** **cutaneous** and **mucocutaneous leishmaniasis**.
- **Miltefosine** ***effective*** in many **Indian Visceral Leishmaniasis regimens** ***including***;
  - * Single dose of Liposomal amphotericin B, in combination with 7 days of oral Miltefosine OR 10 days of Paromomycin.
  - * Miltefosine plus Paromomycin for 10 days.
  - * Miltefosine orally for 28 days OR Paromomycin intramuscularly for 28 days.
- ***Mechanism of action***; is ***not fully*** **understood**.
- ***Dose***; - ≥45 kg: 50 mg orally three times daily for 28 consecutive days.
  - <45 kg: 50 mg orally twice daily for 28 consecutive days.
- **Pregnancy** and **Black Box Warning**; **US FDA pregnancy category D**; ***Adequate*** **methods** of **contraception** *should be* **advised** ***during*** **therapy** and for **5 months** ***after*** **therapy**.
- ***Common side effects***; **Nausea**, **vomiting**, **diarrhea**, ***decreased*** **appetite** and ***increased*** **liver enzymes**.

Chemotherapy for Toxoplasmosis

- **Toxoplasmosis** is a **parasitic disease** caused by ***Toxoplasma gondii***.
- **Infections** *with* **toxoplasmosis** usually cause ***no obvious*** **symptoms** in **adults**.
- **Symptoms** may ***manifest*** and are often **influenza-like** and **fatigue** or **muscle aches** and **pains** that ***last for*** a **month** or **more**.
- ***Rarely*** cause ***decrease*** **immune system function** and ***more*** **likely** to **experience headache**, **confusion**, ***poor*** **coordination**, **seizures** and **lung infections**.
- If **infected** ***during*** **pregnancy**, a **condition** ***known as*** ***congenital*** **toxoplasmosis** may ***affect*** the **child**.



Toxoplasma gondii life cycle

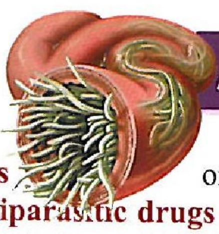
- ***Congenital*** **toxoplasmosis** is ***associated with*** **fetal** ***death*** and ***abortion***, and in **infants**, it is ***associated with*** **neurologic deficits**, **neurocognitive deficits** and **chorio-retinitis**.
- ***Up to*** **half** of the **world's population** is ***infected by*** **toxoplasmosis** but have ***no symptoms***.
- *About* **200,000** cases of ***congenital*** **toxoplasmosis** occur a **year**.
- ***Medications***; **CDC** ***recommendations***;
    - **Non-pregnant** ***patients***; Treatment may be indicated for 2 to 4 weeks.
        - **Pyrimethamine** (100mg loading dose orally followed by 25-50 mg/day) + **Sulfadiazine** (1g orally 4 times daily), OR;
        - **Pyrimethamine** (100mg loading dose orally followed by 25-50 mg/day) + **Clindamycin** (300 mg orally 4 times daily), OR;
        - **Trimethoprim** (10 mg/kg/day)/**Sulfamethoxazole** (50 mg/kg/day) *for* **4 weeks**.
        - * **N.B.**; **Folinic acid** (**Leucovorin**) (10-25 mg/day) ***should be*** **given** to **all patients** to ***prevent*** **hematologic toxicity** of **Pyrimethamine**.
        - * **N.B.**; **Sulfadiazine** or **Clindamycin** can be ***substituted for*** **Azithromycin** 500 mg daily or **Atovaquone** 750 mg twice daily.
    - **Pregnant** ***patients***;
        - **Spiramycin** (1 g orally every 8 hours); for the first and early second trimesters.
        - **Pyrimethamine/Sulfadiazine** and **Leucovorin**; for late second and third trimesters.

Chemotherapy for Giardiasis

- **Giardiasis** (**beaver fever**) is a ***parasitic disease*** caused by ***Giardia lamblia***.
- ***Giardia*** usually ***spreads*** when ***Giardia lamblia*** **cysts** *within* ***contaminate*** **food** or **water**.
- ***Symptoms*** (usually begin 1 to 3 weeks after exposure and without treatment may last up to six weeks);
    - *About* **10%** of those ***infected*** have ***no*** **symptoms**.
    - When **symptoms** occur they may include **diarrhea**, **abdominal pain** and **weight loss**.
    - **Vomiting**, **blood** in the **stool**, and **fever** are ***less*** **common**.
- ***Life Cycle***; (both cysts and trophozoites can be found in feces);
    - In the ***small intestine***, **excystation** ***releases*** **trophozoites** and ***multiply*** in the **lumen** of the ***proximal*** **small bowel**, where they can be ***free*** or ***attached*** to the **mucosa** by a **sucking disk**.
    - **Encystation** ***occurs*** as the **parasites** ***move toward*** the **colon**.
- ***Medications***; **Metronidazole** *for* **5 days** is the ***drug of choice*** (**Tinidazole**, which is ***as effective as*** **Metronidazole** and **Secnidazole** or **Ornidazole** are **also** ***effective***). **Nitazoxanide** is also used.

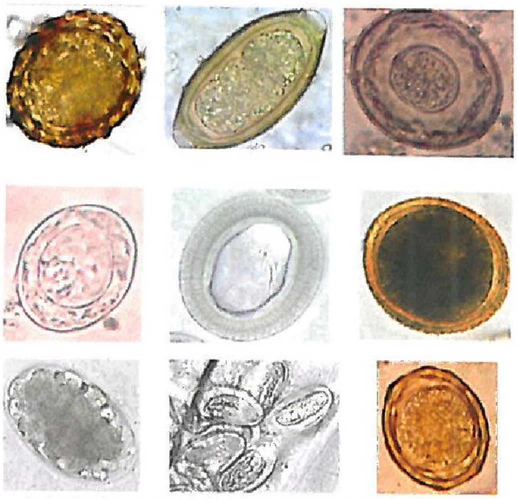
Nitazoxanide (Alinia®)

- **Nitazoxanide** [nye-ta-ZOX-a-nide]; ***nitrothiazole derivative***, **broad-*spectrum*** **antiparasitic**, **antiviral**.
- ***Uses***; **Giardiasis** and **Cryptosporidiosis** and *may use* in **Amebiasis** (Nitazoxanide may effective in Chronic hepatitis B and C in clinical trials).
- ***Usual Adult Dose***; 500 mg twice daily for 3 days.
- ***Common Side Effects***; **Nausea**, **vomiting**, **diarrhea**, **abdominal pain**, **headache** and **chromaturia** (*discolored urine*).



Antihelminthic Drugs

- **Anthelmintics** or **Antihelminthic Drugs** are a *class* of **antiparasitic drugs** that *expel* **parasitic worms (helminths)** and *other* **internal parasites** *from* the **body**.
- **Helminths**, are *large* **multicellular organisms**, which when *mature* can *generally* be **seen** with the *naked* **eye**.
  - They are **worm-*like*** **organisms** *living* in and *feeding* on **living hosts** and *disrupting* their **hosts' nutrient**, causing **weakness and disease.**
- **Helminths** are **live** *inside* the **digestive tract** are called **intestinal parasites**.
  - They are *able to* **survive** in their **mammalian hosts** for *many* **years** due to their *ability* to **manipulate** the **immune response** by *secreting* **immunomodulatory products**.
- **Helminth ova** (or **eggs**) have a *strong* **shell** that *protects* the **eggs** *against* a *range of* **environmental conditions**.



Helminth eggs of different helminth specie

- **Nematodes (Roundworms)**, **Cestodes (Tapeworms)** and **Trematodes (Flukes)** are *three* **major groups** of **helminths** that *infect* **humans**.

Drugs *for the* Treatment *of* Nematodes (Roundworms)

- The **Nematodes** or **Roundworms** is the *second* **largest phylum** in the **animal kingdom**, encompassing *up to* **500,000 species**.
- *Approximately* **60 species** of **Roundworms** *parasitize* **humans**.
- *According* to a **2005 report** by the **WHO**, *approximately* **0.807-1.221 billion** humans have **Ascariasis**, **604-795 million** have **Trichuriasis**, and **576-740 million** have **hookworm infections** worldwide.

Ascaris

- ***Most Common*** **Roundworms** *parasitize* humans;

	Type	Name	Disease
Intestinal Nematode	Hookworms	*Ancylostoma duodenale*	Ancylostomiasis
		Necator americanus	Necatoriasis
	Roundworms	*Ascaris lumbricoides*	Ascariasis
	Pinworms	*Enterobius* (*Oxyuris*) *vermicularis*	Enterobiasis (Oxyuriasis)
	Threadworms	*Strongyloides stercoralis*	Strongyloidiasis
	Whipworms	*Trichuris trichiura*	Trichuriasis
Tissue Nematode		*Ancylostoma braziliense*	Cutaneous Larva Migrans (CLM)
		Trichinella Spiralis	Trichinosis
		Dracunculus medinensis	Dracunculiasis
		Wuchereria bancrofti	Filariasis - Elephantiasis Wuchereriasis - Loiasis
		Brugia malayi and *Brugia timori*	
		Loa loa	
		Dipetalonema perstans	
		Mansonella ozzardi	

Mebendazole (Vermox®)

- **Mebendazole** [me-BEN-da-zole] is a *synthetic* **benzimidazole**, a *broad-spectrum* **antihelminthic agent** was *developed* in **1971**.
- **Mebendazole** is a *first-line* **agent** for the **treatment** *of many types of* **Nematodes** such as; **pinworm** and **hookworm infections**, **ascariasis**, **trichuriasis** and **strongyloidiasis**.
- **Mebendazole** is an *alternative* to **Metronidazole** in **Giardiasis**;
  - ** **Stevens–Johnson syndrome** and the *more severe* **toxic epidermal necrolysis** can occur when **Mebendazole** is *combined with* high *doses* of **Metronidazole**.
- **Benzimidazoles** (**Albendazole**, **Mebendazole** and **Flubendazole**) are **act** *against* **Nematodes** by *inhibiting* the **assembly** of the **cytoplasmic microtubule** in the **parasite** & *blocking* **glucose** *uptake*.
- **Benzimidazoles** are *kills* **hookworm**, **Ascaris**, and *Trichuris* **eggs**; *not need* **dose** *repeated*.
- *Pharmacokinetics*;
  - *Absorption*; *less than* **10%** of **orally** *administered* **Mebendazole** is **absorbed**; **absorption** is *increased* with a **fatty meal**.
  - *Distribution*; **serum**, **cyst fluid**, **liver**, **omental fat**, and **pelvic**, **pulmonary** and **hepatic cysts**.
  - *Protein bound*; 90-95%.
  - *Metabolism*; *rapidly* by the **liver** into **inactive metabolites**.
  - *Excretion*; **urine** and the remainder in the **feces**.
- *Dose*;
  - **Hookworm infections**, **Ascariasis** & **Whipworm** (**trichuriasis**); ≥ 2 years; **100 mg orally** *every* **12 hours** *for* **3 days**, *If cure* is not achieved 3 weeks after treatment, a 2nd course of treatment is advised.
  - **Pinworm** (*Enterobius vermicularis* = **Oxyuriasis**; *Oxyuris*); ≥ 2 years; **100 mg** orally **once** as a *single dose*; this dose *should be* repeated in **2 weeks**.
  - **Giardiasis**; **200 mg orally** *every* **8 hours** *for* **5 days**; as *alternative* to **Metronidazole**.
  - * **Mebendazole 500 mg** can be given as a *single* **dose**.
- *Side Effects*;
  - *Common*; **Diarrhea** and **abdominal pain**
  - *High-dose*; **hypersensitivity reactions** (rash, urticaria), **agranulocytosis**, **alopecia** and *elevated* **liver enzymes**.
- *Pregnancy*; **US FDA pregnancy category C** (Animal studies have revealed evidence of fetotoxicity and teratogenicity) *only* **recommended** for use *during* **pregnancy** when **benefit** *outweighs* **risk**.

Flubendazole (Verm-All®)

- **Flubendazole** is a *fluorinated* **derivative** of **Mebendazole**, *available in* a *number* of **countries**; **two drugs** have **similar** *spectra of activity*, *mechanism*, *doses* and *side effects*.

Thiabendazole or Tiabendazole (Mintezol®)

- **Thiabendazole** [thye-a-BEN-da-zole], a *synthetic* **benzimidazole**, is a *potent broad-spectrum anthelmintic agent*.
- *Because* of its **toxic effects**, *Current use* of **Thiabendazole** as *alternative* to **Ivermectin** or **Albendazole** for **Strongyloidiasis** and **Cutaneous Larva Migrans**; **CLM** (*creeping eruption*).
- **Thiabendazole** is used *as Fungicide* in **fruits** (e.g. **oranges**) and **vegetables**.
- It is also a *chelating agent* in cases of **metal poisoning**, such as **lead**, **mercury** or **antimony** *poisoning*.
- **Thiabendazole** is also used as a *food additive*, a *preservative* with E number **E233**.
- *Dose*;
  - *For* **Strongyloidiasis**; 25 mg/kg twice daily for 2 days, after meals, tablets should be chewed.
  - *For* **Cutaneous Larva Migrans**; **Thiabendazole** 15% **liquid** or **cream** 2 or 3 times daily for 5 days.
- *Side Effects*;
  - *Common*; **Dizziness**, **anorexia**, **nausea** and **vomiting**.
  - *Rare*; **Neuropsychiatric** *symptoms*, *irreversible* **liver failure** and *fatal* **Stevens-Johnson syndrome**.

Pyrantel Pamoate (Pin-X®)

- **Pyrantel pamoate** [pi-RAN-tel PAM-oh-ate] is a *broad-spectrum* **antihelminthic** *highly* **effective** for the *treatment of* **Pinworm**, **Hookworm**, **Ascaris** and **Trichostrongylosis**.
- It is *poorly* **absorbed orally** and *exerts* its **effects** *locally* in the **intestinal tract**.
- *Mechanism of action*; **Pyrantel pamoate** *acts as* a *depolarizing* **neuromuscular blocking** *agent*, causing *release* of **Acetylcholine** and *inhibition* of **cholinesterase**, thereby causing *sudden* **contraction**, *followed by* **paralysis**, of the **helminths**; this has the *result* of causing the **worm** to "*lose* **its grip**" on the **intestinal wall** and is *expelled* **naturally**.
- *Dose*; 11 mg/kg base (maximum 1 g) orally **once** (Hookworm a **3-day** course); repeat dose in 2 weeks.
- *Common Side Effects*; **Nausea**, **vomiting** and **diarrhea**.

Ivermectin (Stromectol®) (Iverzine®)

- **Ivermectin** [eye-ver-MEK-tin] is a ***semisynthetic* macrocyclic lactone**, is a *mixture* of **Avermectin B_{1a}** and **B_{1b}**. It is *derived from* the *soil* **actinomycete** *Streptomyces avermitilis*.
- **Ivermectin** is the ***drug of choice*** for the **treatment** of; **Cutaneous Larva Migrans**, **Strongyloidiasis**, and **Onchocerciasis** (**river blindness**) caused by ***Onchocerca volvulus***.
- It is ***highly effective against*** **Head lice**, **Scabies** and **Lymphatic Filariasis**, ***among* others**.
- **Albendazole–Ivermectin Combination Therapy**; used in **Filariasis**.
- ***Mechanism of action***; **Ivermectin** act by ***binding*** to **glutamate-gated chloride channels** (**GluCls**). **Chloride *influx*** is **enhanced** & **hyperpolarization *occurs***, resulting in **paralysis** & **death** of **worm**.
- **Ivermectin *killing*** of the **microfilaria** in **Onchocerciasis** can result in a ***dangerous*** **Mazzotti Reaction**.
- **Used *only* orally** in **humans** (SC in animals); ***Local* preparations** are ***also* available**.
- ***Usual Doses***; - **Onchocerciasis (river blindness)**; 0.15 mg/kg orally once every 3-12 months.
  - **Strongyloidiasis**; 0.2 mg/kg orally once.
- ***Side Effects***; - **Onchocerciasis**; **Mazzotti Reaction**; **fever**, **headache**, **dizziness**, **somnolence** and **hypotension**; **severity** ***related to*** **parasite load**; **Antihistamines** or/and **Corticosteroids** may be ***given*** to ***decrease*** the **symptoms**.
  - **Strongyloidiasis**; **Fatigue**, **dizziness**, **nausea**, **vomiting**, **abdominal pain** and **rashes**.

Diethylcarbamazine (Hetrazan®)

- **Diethylcarbamazine** [dye-eth-il-kar-BAM-a-zeen] is the ***drug of choice*** for **Filariasis**; ***including*** **Lymphatic Filariasis** (**Elephantiasis**; ***Wuchereria bancrofti***, ***Brugia malayi*** and ***Brugia timori***), **Loiasis** (***Loa loa***) and **Tropical Pulmonary Eosinophilia** (***Wuchereria bancrofti***)
- **Diethylcarbamazine** is ***commonly* used** in ***combination*** with **Albendazole** in **Filariasis**.
- ***Usual Adult Dose***; - Day 1: 50 mg orally.
  - Day 2: 50 mg three times daily
  - Day 3: 100 mg three times daily
  - Day 4-14: 6 mg/kg/day divided into three times daily*.

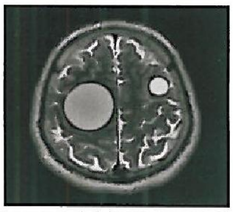
  * In *Loa Loa*; Day 4-21: 9 mg/kg/day divided into three times daily.
- **Antihistamines** or/and **Corticosteroids** may be ***given*** to ***decrease*** **severe reactions** (*due to* release of proteins from dying microfilariae).
- ***Common Side Effects***; **Fever**, **nausea**, **vomiting**, **arthralgia** and **headache**.

Taenia solium

Drugs *for the* Treatment of Cestodes (Tapeworms)

- **Cestodes** (**Tapeworms**) are ***long*, *segmented*** **worms**.
- **Cestodes** and **Trematodes** are worms ***lack*** an **intestinal tract** and ***instead*** can ***absorb*** **nutrients** through their **integument**.
- ***Adult* Cestodes survive *inside*** their **human hosts**, where they are ***limited to*** the **intestinal tract**.
- **Larvae** of ***Echinococcus*** **species *exist within*** the **tissues** and ***migrate*** through ***different* organ systems**, two ***most important*** forms of the **disease** in **humans** are **Cystic Echinococcosis** (**Hydatidosis**) and **Alveolar Echinococcosis**.
- **Echinococcosis** are ***complicated*** to **treat**, *sometimes* ***requiring*** **extensive surgery**.
- ***Most Common*** **Tapeworms *parasitize*** **humans**;

	Type	Name	Primary/Intermediate Host	Disease
Intestinal Cestodes	**Fish worm**	***Diphyllobothrium latum***	**Humans**/Fish	Diphyllobothriasis
	Beef tapeworm	***Taenia saginata***	**Humans**/Cattle	Taeniasis saginata
	Pork tapeworm	***Taenia solium***	**Humans**/Pigs, humans	Taeniasis solium
	Dwarf tapeworm	***Hymenolepis nana***	**Humans**/None	Hymenolepiasis
	Rat tapeworm	***Hymenolepis diminuta***	**Humans**/Rodents	Hymenolepiasis
Tissue Cestodes		***Echinococcus granulosus***	**Dogs**/Humans, sheep	Hydatid disease
		Taenia multiceps ***Taenia serialis***	None/Wild animals	Coenurosis


Intracranial Hydatid Cyst

- **Hydatid disease** is a ***parasitic*** **disease** of **tapeworms** of the ***Echinococcus*** **spp.**
- **2 main *types*** of the disease are **Cystic Echinococcosis** & **Alveolar Echinococcosis**.
- The **disease** is ***spread*** when **food** or **water** that ***contains*** the **eggs** of the ***parasite*** is eaten or by ***close contact*** with an **infected animal** (**Dogs**).
- The **eggs** are ***released*** in the **stool** of ***meat-eating*** **animals** (**dogs**, **foxes** and **wolves**) that are ***infected by*** the **parasite**; i.e., **Animals** to ***become*** **infected** (**dogs**) they ***must*** **eat** the **organs** of an **animal** that ***contains*** the **cysts** such as **sheep** or **rodents**.
- The **symptoms** and **signs** that occur ***depend on*** the **cyst's location** and **size**.

Niclosamide (Yomesan®)

- **Niclosamide** [ni-KLOE-sa-mide] **now** is a ***second-line* drug** (*alternative to* **Praziquantel**) for the *treatment* of ***most*** **Cestode infections**, ***no longer*** **available** in **USA** ***according to*** **CDC** *recommendations* (***using*** **Praziquantel**; as **single dose**).
- **Niclosamide** ***rapidly*** **kill adult worms** (*but **not*** **ova**) by *causing* **necrosis** of the **head** and **adjoining segments** of the **tapeworm**, *due to **inhibition*** of **oxidative phosphorylation** or ***stimulation*** of **ATPase** ***activity***.
- ***Dose***; **500 mg Chewable Tablet** (*in* **foil cover**);
  - **Beef tapeworm** (***Taenia saginata***), **Pork tapeworm** (***Taenia solium***) and **Fish tapeworm** (***Diphyllobothrium latum***); **One *single*** **dose** is ***sufficient***;
    - < 2 years; 1 tablet (500 mg) - 2-6 years; 2 tablets - >6 years; 4 tablets
  - **Dwarf tapeworm** (***Hymenolepis nana***); **7 days** is *recommended*; **Praziquantel** is ***superior***;
    - **First day**: - < 2 years; 1 tablet (500 mg) - 2-6 years; 2 tablets - >6 years; 4 tablets
    - *Another* **six days**: - < 2 years; 1/2 tablet - 2-6 years; 1 tablets - >6 years; 2 tablets
- ***Precautions***; * ***Don't* remove *from*** **foil *until*** *immediately* ***before*** **administration.**

  * **Tablets *should be administered*** in the **morning** on an ***empty*** **stomach.**

  * **Tablets *should be*** **chewed** *before* **swallowing** and **washed down** with a ***little*** **water.**

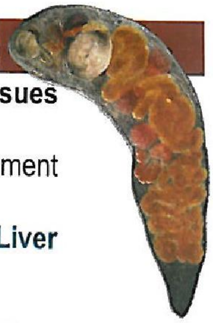
  * **Patients *should*** receive a **saline purgative** (e.g. **Sodium sulfate**, **Magnesium sulfate**) **2 hours *after*** the **Yomesan®**; to **ensure** a ***rapid*** and ***complete*** **expulsion** of the **worm.**

  * **Alcohol *should be*** **avoided *within*** **1 day** of **Niclosamide *use*.**
- **Niclosamide** may be given ***safely*** in **pregnancy** (**Category B**) and to **patients *with*** **liver**, **biliary** and **kidney *diseases***.
- ***Common Side Effects***; ***Mild*** **GI disturbances** (Nausea, vomiting, diarrhea & abdominal discomfort).

Albendazole (Albenza®)

- **Albendazole** [al-BEN-da-zole], is a **broad-spectrum** ***benzimidazole*** **antihelminthic** (**Benzimidazole Carbamate**) **effective** ***against many types*** *including*; **Cestodes** and **Nematodes**.
- It is the ***drug of choice*** of **Hydatid Disease** and **Cysticercosis** (**Tissue Cestodes**).
- It is ***also*** **used** in the *treatment of **many types*** *of* **Nematodes** such as; **Pinworm** and **Hookworm infections**, **Ascariasis**, **Trichuriasis** and **Strongyloidiasis**.
- **Albendazole** is an ***alternative*** or ***adjunct*** to **Metronidazole** in **Giardiasis *especially in*** **children.**
- **Benzimidazoles** (**Albendazole**, **Mebendazole** and **Flubendazole**) are *thought to* **act *against*** **Nematodes** by ***inhibiting*** **cytoplasmic microtubule synthesis** and **glucose *uptake***.
- **Albendazole** also has **larvicidal *effects*** in **Hydatid Disease**, **Cysticercosis**, **Ascariasis** and **Hookworm infection** and **ovicidal *effects*** in **Ascariasis**, **Ancylostomiasis** and **Trichuriasis**.
- **Albendazole** is **used** in ***combination*** with **Diethylcarbamazine** or **Ivermectin** in **Filariasis**.
- ***Pharmacokinetics***;
  - ***Absorption***; ***Erratically*** **absorbed** *after* **oral administration**, *but* **absorption** is ***enhanced*** by a ***high*-fat meal** (***up to*** **4-5 times**).
  - ***Distribution***; ***Widely*** **distributed**; ***inside*** **hydatid cysts** and **CSF**.
  - ***Metabolism***; ***Extensive*** **first-pass *effect*** (***rapid*** **sulfoxidation**); **Albendazole sulfoxide** (***active***).
  - ***Excretion***; ***Active*** **metabolites** are ***excreted*** in the **urine**.
- ***Doses***; - **Neurocysticercosis** (***Taenia Solium*** **Cyst** in the **brain**);
    - >60 kg: 400 mg orally twice daily with meals for 8-30 days.
    - <60 kg: 15 mg/kg/day orally in divided doses twice a day with meals for 8-30 days (Max.800 mg/day).
  - **Hydatid Disease**;
    - >60 kg: 400 mg orally twice daily with meals for 28 days, THEN 14 drug-free days for 3 cycles.
    - <60 kg: 15 mg/kg/day orally in divided doses twice a day with meals for 28 days, THEN 14 drug-free days x 3 cycles (Max.800 mg/day).
  - **Ancylostoma**, **Ascariasis**, **Hookworm**, **Trichostrongylus**; 400 mg orally once.
  - **Pinworm**; 400 mg orally once, repeat in 2 weeks.
- ***Common Side Effects***; ***Mild*** and ***transient***; **Headache** and **nausea**.
- ***Long term therapy*** (**Hydatid Disease**; **3 months**); ***risk*** of **hepatotoxicity** and, *rarely*, **agranulocytosis** or **pancytopenia** (drop in white blood cells, red blood cells and platelets).
- ***Pregnancy***; **US FDA category C** and **category D** in **Australia**; ***only*** **recommended** for use ***during*** **pregnancy** when **benefit *outweighs*** **risk**.

Drugs for the Treatment of Trematodes (Flukes)



- **Trematodes** (**Flukes**) are ***leaf-shaped* Flatworms** that are ***generally*** *characterized by* the **tissues** they **infect** (*for example*, **liver**, **lung**, **intestinal** or **blood**).
- The **parasites** are so named because of their *conspicuous* **suckers**, the organs of attachment (trematos means "**pierced** *with* **holes**").
- ***Depending on*** the **habitat** in the *infected* **host**, **flukes** can be classified as **Blood Flukes**, **Liver Flukes**, **Lung Flukes**, or **Intestinal Flukes**.
- ***Most Common*** **Trematodes** ***parasitize*** **humans**;

Type	Name	Disease
Liver Flukes	***Fasciola gigantic***	Fascioliasis or Liver-rot
	Fasciola hepatica	
Intestinal Flukes	***Heterophyes heterophyes***	Heterophyiasis
Blood Flukes	***Schistosoma haematobium***	Urinary bilharziasis (Schistosomiasis)
	Schistosoma mansoni	Intestinal bilharziasis (Schistosomiasis)
Lung Flukes	***Paragonimus***	Paragonimiasis

Praziquantel (Biltricide®)

- **Praziquantel** [pray-zi-KWON-tel] is a ***drug of choice*** for the treatment of ***all forms*** of **Schistosomiasis**, other **Trematode Infections** and **Cestode Infections** ***such as*** **Taeniasis** *including* **Cysticercosis**.
- The **drug's** **safety** and **effectiveness** as a ***single*** **oral dose** have also ***made*** it **useful** in mass ***treatment of*** **several infections**.
- **Praziquantel** acts by ***increase*** **cell membrane *permeability*** to **Calcium**, *causing* **contracture** and **paralysis** of the **parasite**.
- **Praziquantel** ***should be*** **taken** *with* **food** (**not chewed** *due to* a **bitter taste**).
- It is ***rapidly*** **absorbed** after **oral administration** and ***distributes*** into **CSF**.
- The drug is ***extensively*** **metabolized**, and the ***inactive*** **metabolites** are **excreted *primarily*** in the **urine**.
- ***Doses***; - **Schistosomiasis**; 20 mg/kg/dose orally in 3 doses (4-6 hrs) for 1 day.
  - **Clonorchiasis**, **Opisthorchiasis** and **Paragonimiasis**; 25 mg/kg/dose 3 times daily for 2 days.
  - **Taeniasis** and **Diphyllobothriasis**; 5-10 mg/kg orally once (nearly 100% cure rates).
  - **Tapeworms**; 5-10 mg/kg as ***single dose*** or 25 mg/kg if ***Hymenolepis nana***.
- ***Side Effects***; - ***Common***; **Dizziness**, **malaise**, **headache** and **GIT disturbance**.
  - *Mild* and *transient* ***elevations*** of **liver enzymes** *may occur*.
  - ***Low-grade*** **fever**, **pruritus** and **skin rashes**, may associated with **eosinophilia** (probably due to the release of proteins from dying worms rather than direct drug toxicity).
- ***Drug Interactions***; - **Corticosteroids**, **Phenytoin**, **Rifampin** and **Carbamazepine** may ***increase*** the **metabolism** of **Praziquantel**; ***decreased*** **Praziquantel *levels***.
  - **Cimetidine** causes ***increased*** **Praziquantel *levels***.
- ***Contraindications***; **Praziquantel** is ***contraindicated*** for the **treatment** of **Ocular Cysticercosis**, ***because*** **destruction** of the **organism** in the **eye** may cause ***irreversible*** **damage**.

Other Anthelmintics Drugs

Oxamniquine (Vansil®)

- **Oxamniquine** [ox-AM-ni-kwin] is a ***semisynthetic*** **Tetrahydroquinoline** used as ***alternative to*** **Praziquantel** for the **treatment** of ***Schistosoma mansoni*** **infections**. The drug ***may cause*** **seizures**.

Metrifonate or Trichlorfon

- **Metrifonate** [ME-try-FO-nate] is an ***irreversible*** **organophosphate** (**cholinesterase inhibitor**; paralyzes the adult worms) used as ***alternative to*** **Praziquantel** for the **treatment** of ***Schistosoma haematobium***.

Piperazine

- **Piperazine** [pi-PER-a-zeen] is an ***alternative*** for the **treatment** of **ascariasis**,

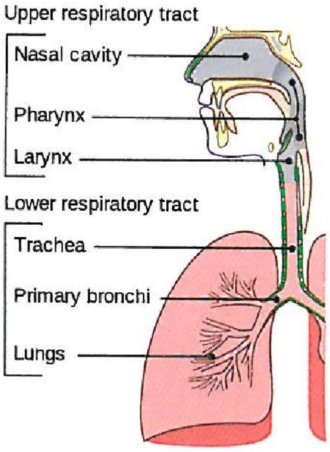
Levamisole (Ergamisol®) (Katrex®)

- **Levamisole** [leave-AH-mah-sole] is an ***anthelmintic/immunomodulator drug***, used as ***alternative*** for the **treatment** of **Ascariasis** and **Hookworm infections**.

Common Infectious Diseases

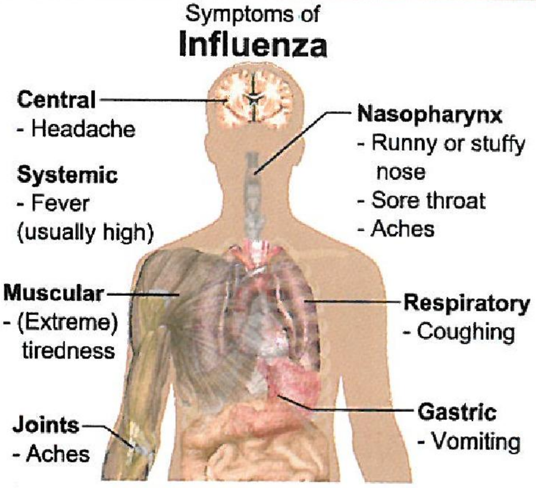
A) Respiratory Tract Infections (RTIs)

- **Respiratory Tract Infections (RTIs)** *further* **classified as** an;
  - **A) Upper Respiratory Tract Infections (URTIs); Tonsillitis, Pharyngitis, Laryngitis, Sinusitis, Otitis Media** and **Common Cold**;
    - **URTI represents** the ***most common* reasons** for **doctor visits**.
    - The ***majority*** of **URTIs** are *caused by* **viruses** & ***self-limited***.
    - **URTIs** can **happen** at ***any time***, they are ***most common*** in the **fall** and **winter** months, from **September** *until* **March**.
  - **B) Lower Respiratory Tract Infections (LRTIs); Bronchitis** and **Pneumonia**;
    - **LRTIs** are a **leading *cause*** of **sickness** and **mortality** *both* in **children** and **adults *worldwide***.
    - **LRTIs** are **generally *more serious*** *than* **upper respiratory infections**.


Upper respiratory tract
Nasal cavity
Pharynx
Larynx
Lower respiratory tract
Trachea
Primary bronchi
Lungs

I) Influenza

- **Influenza**, **one** of the ***most common*** **infectious diseases**.
- **Characteristics of influenza infection**;
  - ***Highly*** **contagious airborne disease**.
  - ***Seasonal*** **epidemic** with ***significant*** **mortality**.
  - ***Reaches peak*** **prevalence** in **winter**.
  - ***Average*** **overall attack *rates*** of **10–20%**.
  - **Mortality *greatest*** in those ***older than*** **65 years** (especially with heart and lung disease): More than 80% of deaths caused by influenza are from this age group (20,000 deaths a year in the United States).
- **Influenza virus *strains*** are *classified by their*; **core proteins** (ie, **A**, **B** or **C**), **species** of **origin** (eg, **avian**, **swine**) and **geographic site** of ***isolation***.


Symptoms of
Influenza
Central
- Headache
Systemic
- Fever
(usually high)
Muscular
- (Extreme)
tiredness
Joints
- Aches
Nasopharynx
- Runny or stuffy nose
- Sore throat
- Aches
Respiratory
- Coughing
Gastric
- Vomiting

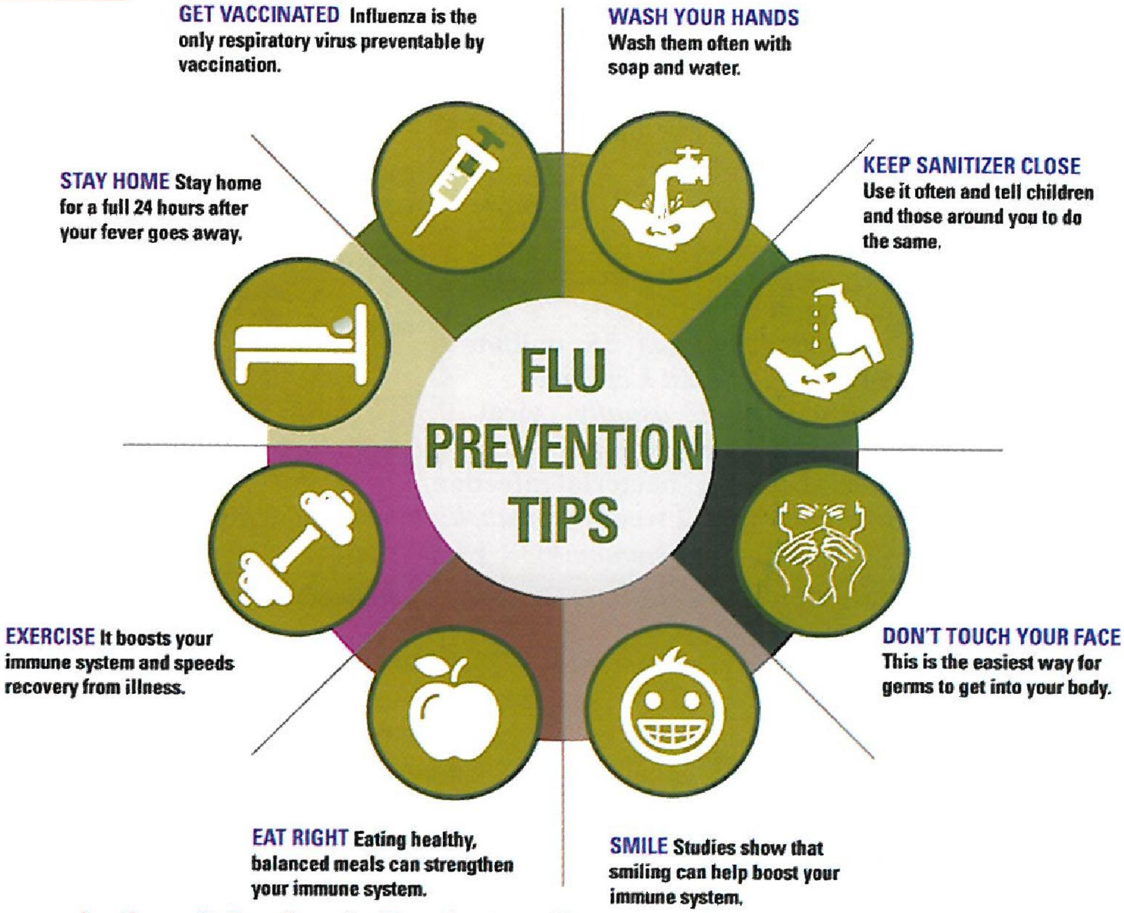
- **Influenza A** and **Influenza B** can cause **Epidemics** (country).
- **Influenza A**, the ***only*** **strain** that causes **Pandemics** (continent).
- The **common cold**, is ***another*** **viral infectious disease** of the **upper respiratory tract**, ***over*** **200 virus *strains*** are ***implicated*** in the cause of the **common cold** (***rhinoviruses*** are the ***most common***).
- It can be ***difficult*** to ***distinguish*** *between* the **common cold** and **influenza** in the ***early*** **stages** of *these* **infections**;

Signs and Symptoms	Influenza (Flu)	Common Cold (Cold)
Onset	Sudden	Gradual
Temperature	High (>38°C) of 3–4 days duration	Occasional
Cough	Dry (can become severe)	Hacking*
Headache	Prominent	Occasional
Myalgia (muscle aches & pains)	Usual; often severe	Slight
Tiredness and weakness	Can last 2–3 weeks	Very mild
Extreme exhaustion	Early and prominent	Never
Chest discomfort	Common	Mild to moderate
Stuffy nose	Sometimes	Common
Sneezing	Sometimes	Usual
Sore throat	Sometimes	Common

* Hacking cough; a small and frequent cough, usually short and dry; a broken cough with a rough and loud sound.

- **Influenza A**; *several* **subtypes** are **labeled** *according to* an **H** number (for the type of hemagglutinin) and an **N** number (for the type of neuraminidase), e.g., **H1N1**, **H3N2**.
  - **Influenza A viruses changing**; They can *change* in *two* **different ways**;
    - A) **Antigenic Drift**; *Gradual* **small changes** in the **genes** of **influenza viruses** that **happen** *continually over time* as the **virus replicates** (**annually**)
    - B) **Antigenic Shift**; *Abrupt*, **major change**, *resulting* in *new* **hemagglutinin** and/or *new* **hemagglutinin** and **neuraminidase proteins**.
  - **Influenza A viruses** *causes* **epidemics** *every* **1–3 years**.
- **Influenza B**; carries **one** *form* of **hemagglutinin** and **one** *form* of **neuraminidase, both** of which are *less* **likely** to **mutate** *than* **influenza A**; *Changes through* **Antigenic Drift** (*Causes* **epidemics** *every* **5 years**).
- **Persons** at *higher* **risk** for **influenza complications** *include*;
  - **Patients *younger than* 2 years or 65 years and *older*.**
  - **Patients** with **chronic disease states**: **Pulmonary** (*including* asthma), **cardiovascular** (*except* hypertension alone), **renal**, **hepatic**, **hematologic** (*including* sickle cell disease), **metabolic disorders** (*including* diabetes mellitus), or **neurologic** and **neurodevelopment** *conditions*.
  - **Immunosuppressed patients**.
  - **Pregnant women**.
  - **Patients** *younger than* **19 years** who are *receiving long-term* **aspirin therapy** (*risk for* **Reye's syndrome**).
  - **American Indians** and **Alaska Natives**.
  - **Patients** who are *morbidly* **obese**.
  - *Residents* of **nursing homes** and **other** *long-term* **care facilities**.
- **Pharmacotherapy** (*Recommendations*);
  - *Early* **antiviral treatment** can *reduce* the *risk of* **complications** from **influenza** (e.g., **pneumonia**, **respiratory failure**, and **death**);
    - *Should be* **started** *as soon as* **possible** *after* **illness** *onset*.
    - *Greatest* **benefit** is when **antiviral treatment** is *started within* **48 hours** of **influenza illness** *onset*.
  - **Antiviral treatment** is *recommended* as **early** *as possible* for *any* **patient** *with* **confirmed** or **suspected influenza** *who*;
    - — is **hospitalized**;
    - — has *severe, complicated*, or *progressive* **illness**; or
    - — is at *higher risk* for **influenza complications** (see above).
  - **Antiviral treatment** also can be *considered for* any *previously* **healthy**, **symptomatic patient** *without* **risk factor** with *confirmed* or *suspected* **influenza** on the basis of **clinical judgment** (*must initiate within* **48 hours**).
  - *Recommended* **antiviral medications**; **ONLY** **Neuraminidase Inhibitors** (**NAIs**); **Oseltamivir** OR **Zanamivir**; **Initiate** *within* **48 hours** of **symptom** *onset*.
    - *Doses*;
      - **Oseltamivir** (Tamiflu®); *Duration of therapy*: **5 days**;
        - <15 kg: 30 mg *orally* twice daily.
        - 15-23 kg: 45 mg *orally* twice daily.
        - 23-40 kg: 60 mg *orally* twice daily.
        - >40: 75 mg *orally* twice daily.
      - **Zanamivir** (Relenza®); **10 mg** (**2** *inhalation tab.*) **twice** for **5 days**.
    - *Side effects*;
      - **Oseltamivir**; **GI discomfort** and **nausea** (can *decreased* by **taking** *with* **food**).
      - **Zanamivir**; **Headache**, **throat/tonsil pain** and **cough**.
  - **Chemoprophylaxis**; **ONLY** for **influenza-related complications** in **patients** at *very* **high risk** (e.g., *severely* **immunosuppressed patients**) who *cannot* be *protected by* the **vaccine** when a *high risk* of **exposure exists**; **ONLY** **Neuraminidase Inhibitors** (**NAIs**); **Oseltamivir** OR **Zanamivir** (**Amantadine** and **Rimantadine**: *Not recommended* for **prevention** because of *current* **universal resistance**);
    - **Pre-exposure Chemoprophylaxis**; For **4-6 weeks** *during* peak **influenza season**.
    - **Post-exposure Chemoprophylaxis**; **No** *more than* **10 days**.
      - **Oseltamivir** (Tamiflu®) and **Zanamivir** (**Relenza**®); Dosages for **chemoprophylaxis** are the *same* for **treatments**, but doses are administered **ONLY once** per day *rather than* **twice**.

- **Prevention**;



GET VACCINATED Influenza is the only respiratory virus preventable by vaccination.

WASH YOUR HANDS Wash them often with soap and water.

STAY HOME Stay home for a full 24 hours after your fever goes away.

KEEP SANITIZER CLOSE Use it often and tell children and those around you to do the same.

EXERCISE It boosts your immune system and speeds recovery from illness.

DON'T TOUCH YOUR FACE This is the easiest way for germs to get into your body.

EAT RIGHT Eating healthy, balanced meals can strengthen your immune system.

SMILE Studies show that smiling can help boost your immune system.

- **Immunizations *Related to the* Respiratory Tract**;
  - **A) Pneumococcal vaccines**; CDC *recommends* **Pneumococcal Conjugate Vaccine** for;
    - *All children* <2 years old.
    - *All adults* ≥ 65 years old.
    - People 2-64 years old *with certain* medical conditions.
  - **Pneumococcal Polysaccharide Vaccine (PPSV23)** (Pneumovax®23);
    - **PPSV** *contains* 23 purified *capsular* polysaccharide antigens of ***Streptococcus pneumoniae***.
    - The 23 capsular *types* account for 85–90% of *invasive* ***S. pneumoniae*** infection.
    - Antibody *levels* remain *elevated* for *at least* 5 years.
  - **Pneumococcal Conjugate Vaccine (PCV13)** (Prevnar-13®);
    - **PCV** *contains* 13 purified *capsular* polysaccharide antigens of ***S. pneumoniae*** conjugated to a carrier protein.
    - The 13 capsular *types* are *all* in PPSV23 *except* for one.
    - If both **PCV13** and **PPSV23** are *required*, **PCV13** *should be* given *first*, *followed by* **PPSV23** *at least* 8 weeks *later*. If **PPSV23** is *given* first, **PCV13** *should be* given *at least* 6–12 months *later*.
    - **PCV13** is *routinely* (Vaccination Schedule) given to children at 2, 4, 6, and 12–15 months of *age*.
    - *Single* revaccination of **PCV13** *recommended after* 5 years.
  - **B) Seasonal Flu Vaccine (Flu Shots)**;
    - WHO & CDC *recommend* yearly *vaccination* for *nearly all* people ≥ 6 months, *especially* those at high risk.
    - *Each year*, **3 strains** are *chosen* for selection in that year's flu vaccination by the WHO.
    - The *chosen* strains are the H1N1, H3N2, and Type-B strains thought *most likely* to cause *significant* human suffering in the coming season.
    - The vaccines are *generally* safe (**Fever** may occurs in **children** vaccinated; 5-10%).
    - Vaccines are manufactured *using* virus *grown in* **eggs**; It *should not* be given to those with *severe* allergies to eggs or to *previous* versions of the vaccine.
    - **Dose**; - 6-35 months (3 years); 0.25 mL *once* yearly (*second* injection 0.25 mL with 1 month *interval only* in first time of vaccination).
      - 3-8 years; 0.5 mL *once* yearly (*second* injection 0.5 mL with 1 month *interval only* in first time of vaccination).
      - ≥ 9 years; 0.5 mL *once* yearly.

II) Sinusitis (Sinus Infection or Rhinosinusitis)

HEALTHY SINUS
SINUSITIS
Frontal Sinus
Inflamed Sinus Lining
Sphenoid Sinus
Ethmoid Sinus
Septum
Excess Mucus/ Sinus Infection
Maxillary Sinus

- **Sinusitis** is ***inflammation*** of the **mucosal *lining*** of the **nasal passage & paranasal sinuses *lasting up*** to **4 weeks.**
- **Causes**; *including* **viruses** (more than 90%), **bacteria** (less than 10%) and **fungi.**
- ***Streptococcus pneumoniae*** and ***Haemophilus influenzae*** are ***common* bacterial pathogens.**
- ***Common* signs** and **symptoms** include ***thick* nasal mucus**, a ***plugged* nose**, and **pain** in the **face.**
- **Prevalence**; ***Current* estimates** are that **35 million Americans *each year* experience *at least* 1 *episode*.**
- **Acute sinusitis** (***last up to* 4 weeks**); ***usually* viral** (common cold or influenza); ***lasts up to* 10 days** and that ***completely* resolves** in **99% *of* cases.**
- **Chronic sinusitis** (***last up to* 12 weeks**); **bacterial infection.**
- **Subacute sinusitis** (*lasts between* **4 & 12 weeks**); a ***transition*** *between* **acute** and **chronic infection.**
- **Diagnosis**; ***Presence*** of at ***least* 2 major *symptoms*** OR **1 major** and **2** or **more minor symptoms**;

Major Symptoms	Minor Symptoms
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis (Bad breath)
Facial congestion or fullness	Dental pain
Facial pain or pressure	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

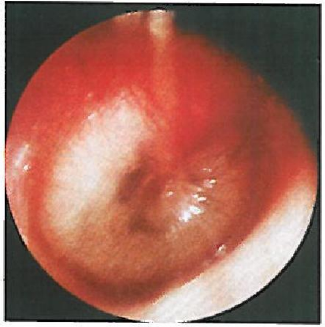
- **Differentiating Viral *from* Bacterial Sinusitis**;

	Viral	Bacterial
Symptoms	Nasal discharge, congestion and scratchy throat.	
Nasal discharge	Clear *to* purulent *to* clear; Purulence not present until days 4–5	Persistent purulent discharge (>10 days) or early and severe (first 3–4 days) or increased on days 5–6 after typical viral infection (double-sickening)
Fever	None (or early in course, resolving in 48 hours)	High temperature (≥39°C) and early (first 3–4 days)
Other symptoms	Headache, facial pain, and myalgia (resolving in 48 hours)	Headache, facial pain, myalgia, daytime cough
Peak symptoms	Days 3–6	Persistent >10 days or early and severe (first 3–4 days) or improved symptoms that worsen on days 5–6
Duration	5–10 days	In general; >10 days

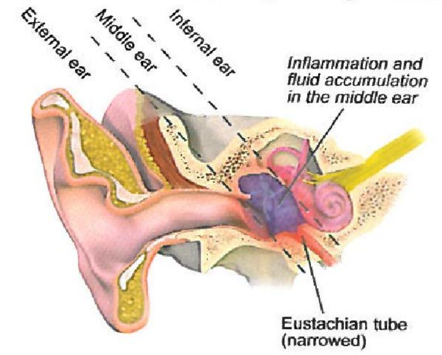
- **Pharmacotherapy (*Recommendations*); Acute Bacterial Sinusitis**
  - ***First-line* therapy; Amoxicillin/Clavulanate (Augmentin®).**
  - ***High-dose* Amoxicillin/Clavulanate; 2 g *twice* daily** in **adults (Augmentin® XR)** or **90 mg/kg/day** *divided* ***twice* daily (Augmentin® ES-600)** in;
    1) Geographic regions with high endemic rates (>10%) of invasive penicillin-non-susceptible *S. pneumoniae*.
    2) Those with a severe infection (e.g., evidence of systemic toxicity with a temperature of 39°C or higher and a threat of suppurative complications).
    3) Attendance at day care.
    4) Age <2 years OR >65 years.
    5) Recent hospitalization.
    6) Antibiotic use within the past month.
    7) Those who are immunocompromised.
  - ***Second-line* therapy**;
    - **Respiratory fluoroquinolone** (*including* **children** with **type I hypersensitivity to Penicillin**).
    - **Doxycycline**
    - **Cefixime** OR **Cefpodoxime** *with* **Clindamycin** (for ***children*** with **non–type I hypersensitivity to Penicillin**).
    - ***Intranasal* saline irrigation** as adjunctive therapy.
    - ***Intranasal* corticosteroids** as adjunctive therapy in ***patients with* allergic rhinitis.**
- ***Duration of therapy***; ***Adults*: 5–7 days** - ***Children*: 10–14 days.**

III) Acute Otitis Media (AOM)

- **Otitis media (OM)** is ***any* inflammation** of **middle ear**, *without* **reference** to **etiology** or **pathogenesis**.
- The ***term* Otitis Media** *comes from* the ***Latin* oto** - for "**ear**," - **itis** for "**inflammation**," and **medi-** for "**middle**".
- It is ***very common*** in **children**.
- **Acute Otitis Media** is the ***second*** **most common *disease*** of **childhood**.
- **Vaccination *against* influenza** and **pneumococcus** may ***decrease*** the **risk** of **Acute Otitis Media**.



Acute Otitis Media



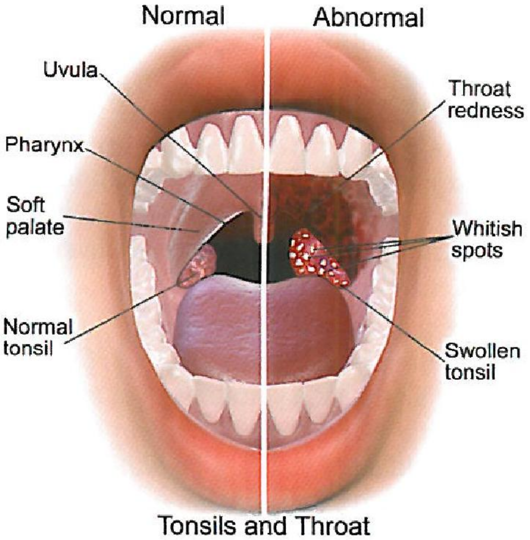
External ear
Middle ear
Internal ear
Inflammation and fluid accumulation in the middle ear
Eustachian tube (narrowed)

- There are ***several*** **subtypes** of;
  - **Acute Otitis Media (AOM)**; ***Convention*** as the ***first* 3 weeks** of a ***process*** in which the **middle ear** *shows* the **signs** and **symptoms** of ***acute*** **inflammation**.
  - **Otitis Media *with* Effusion (OME)** or **Serous OM** or **Secretory OM**; ***Non-purulent*** **effusion** of the **middle ear** that may be ***either*** **mucoid** or **serous**, typically ***do not*** involve **pain** or **fever** and *occur **during*** the ***resolution*** of **AOM**, ***once*** the **acute inflammation** has ***resolved***.
  - **Chronic Suppurative Otitis Media (CSOM)**; A ***perforated*** **tympanic membrane** with ***persistent*** **drainage** ***from*** the **middle ear** (***lasting*** **> 6-12 weeks**).
  - **Adhesive Otitis Media**; The **tympanic membrane** is ***bound*** **partially** or **totally** to the **medial wall** of the **middle ear** by ***fibrous*** **adhesions**, causing **conductive hear loss**.
- **Causes**; - **40-75%** of **Acute Otitis Media** are *caused by* **viral** **pathogens**.
  - ***Common*** **bacterial pathogens**; ***Streptococcus pneumoniae*** (25–50%), ***Haemophilus influenzae*** (15–30%), and ***Moraxella catarrhalis*** (3–20%).
- **Pathophysiology**; The **infection** is ***usually*** of **viral origin**, *but* **allergic** and other **inflammatory *conditions***, ***involving*** the **Eustachian Tube** (**ET**) may create a ***similar*** **outcome**, the **gas volume** in the ***middle ear*** is **trapped** and ***slowly*** **absorbed** by the ***surrounding*** **tissues**, leading to ***negative*** **pressure** in the **middle ear**, by ***reflux*** or ***aspiration*** of ***unwanted*** **secretions** from the **nasopharynx** *into the* **normally sterile middle-ear space**, **bacteria** that ***colonize*** the **nasopharynx** enter the **middle ear** and are ***not cleared*** **properly** by **mucociliary system**. **Children** tend to be ***more*** **susceptible** to **otitis media** *than* **adults** *because* the **anatomy** of their **Eustachian Tube** is ***shorter*** and ***more*** **horizontal**, *facilitating* **bacterial *entry*** *into* the **middle ear**.
- **Diagnosis**; A **diagnosis** of **Acute Otitis Media** ***requires***;
  - **1**) A **history** of ***acute*** **onset** of **signs** and **symptoms**,
  - PLUS **2**) The ***presence*** of **middle-ear effusion**; indicated by **any** of the following;
    - Bulging of the tympanic membrane.
    - Limited or absent mobility of the tympanic membrane.
    - Air fluid level behind the tympanic membrane.
    - Otorrhea
  - PLUS **3**) ***Signs*** and ***symptoms*** of **middle-ear *inflammation***; indicated by **either**;
    - A) Distinct erythema of the tympanic membrane.
    - OR B) Distinct otalgia (discomfort clearly referable to the ear[s] that results in interference with or precludes normal activity or sleep).
- **Pharmacotherapy** (***Recommendations***); **Acute Otitis Media**
  - * **Pain Management** (**Paracetamol** or **NSAIDs**); ***especially*** *during* the ***first*** **24 hours** of an ***episode*** of **AOM**, ***should be*** *addressed* ***regardless*** of the *use of* **antibacterial agents**.
  - * **Antibiotic therapy**;

	Initial Diagnosis		Failure at 48–72 Hours	
	Non-severe	**Severe**	**Non-severe**	**Severe**
First line	Amoxicillin; *high-dose*; 80–90 mg/kg/day divided twice daily	Amoxicillin-Clavulanate; *high-dose*; 90 mg/kg/day divided twice daily	Amoxicillin-Clavulanate; *high-dose*; 90 mg/kg/day divided twice daily	Ceftriaxone (1–3 days)
Non–type 1 allergy	Cefdinir, Cefuroxime, Cefpodoxime	Ceftriaxone (1–3 days)	Ceftriaxone (1–3 days)	Clindamycin
Type 1 allergy	Azithromycin, Clarithromycin	Clindamycin	Clindamycin	Clindamycin

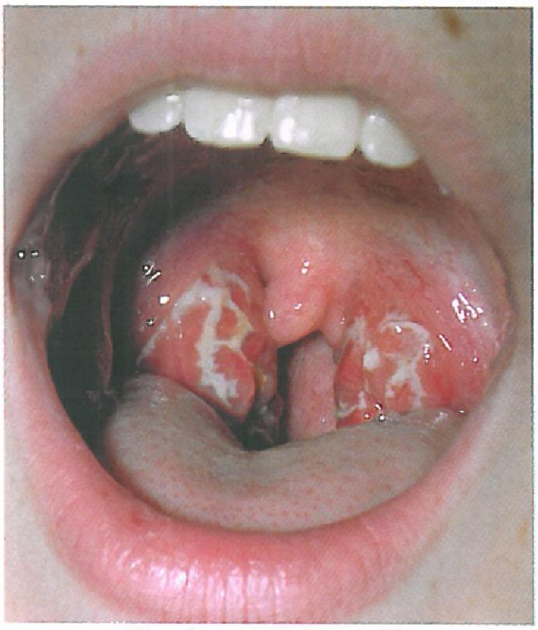
IV) Acute Pharyngitis

- **Pharyngitis** is *inflammation* of the **back** of the **throat** (**pharynx** or **tonsils**). It **typically** *results* in a **sore throat** and **fever**.
- **Causes**; *usually* **infectious**, with *most cases* being of **viral** *origin* and *most* **bacterial** *cases attributable to* ***Streptococcus pyogenes*** (**Group A *Streptococcus*** [**GAS**] OR **Group A *β*-hemolytic Streptococci** [**GABHS**]). Other causes include allergy, trauma, toxins, and neoplasia (***bacterial*** **causes**, *known as* **strep throat**).
- **Seasonal outbreaks** *occur*, and the *incidence* of **GAS** is *highest* in **winter** and *early* **spring**.
- **Children ages 5-15 years** are *most* **susceptible**.
- It is **spread** by *direct, close* **contact** with *infected* **person**.
- **Complications**;
  - **Non-suppurative**; such as **acute rheumatic fever**, **acute glomerulonephritis**, and **reactive arthritis**.
  - **Suppurative**; such as **peri-tonsillar abscess**, **retropharyngeal abscess**, **cervical lymphadenitis**, **mastoiditis**, **otitis media**, **sinusitis**, and **necrotizing fasciitis**.



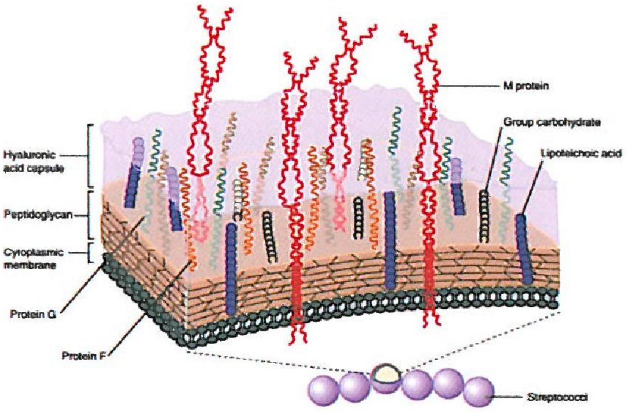
Tonsils and Throat

Acute rheumatic fever is rarely seen in developed countries. In the United States, acute rheumatic fever secondary to GAS infection was a cause of concern in the 1950s and was the major reason for penicillin therapy, but the annual incidence of this disease today is extremely rare (≤1 case per 1 million population). However, some risk does remain.



Streptococcal pharyngitis

- **Pathophysiology**;
  - *β*-hemolytic streptococci have the ability to cause large zones of hemolysis on blood agar (aiding in microbiological identification), which contains group A antigens; is the most common species referred to as a group A *β*-hemolytic streptococci (GABHS).
  - The most important virulence factor of GABHS is the M protein.



- This protein, located peripherally on the cell wall, is required for invasive infection.
- T cells exposed to this M protein are postulated to cross-react with similar epitopes on human cardiac myosin and laminin, contributing to the pathogenesis of rheumatic heart disease.
- Currently, more than 100 M protein serotypes have been identified, and a molecular approach to identification of emm (M protein) genes has been achieved.
- This protein provides a potential target for a GABHS vaccine, although successful widespread implementation of such a vaccine remains elusive.
- GABHS contains a hyaluronic acid capsule, which also plays an important role in infection.
- Adhesins enable GABHS attachment at sites such as the pharynx. This attachment allows for colonization and competition with normal host flora.
- Some strains produce erythrogenic toxins, which cause the rash of scarlet fever in susceptible hosts.
- GABHS accounts for 15%-30% of pharyngitis cases in children and 5%-10% of cases in adults.
- In children about 12% carry GAS in their pharynx without any signs or symptoms, and after treatment, about 15% of those remain positive.
- Effective antibiotic therapy reduces the infectious period to about 24 hours; patient is no longer considered contagious.

- **Diagnosis**;* **Modified Centor Criteria** for ***Clinical Prediction*** of **Group A *β*-Hemolytic Streptococcal Pharyngitis**;

Criteria	Points
Temperature >38°C (101°F)	1
Absence of cough	1
Swollen, tender anterior cervical nodes	1
Tonsillar swelling or exudate	1
Age;	
3–14 years	1
15–44 years	0
45 years or older	−1

Score	Risk of streptococcal infection
≤0	1–2.5%
1	5–10%
2	11–17%
3	28–35%
≥4	51–53%

Centor Criteria

* **Laboratory testing**; ***should not*** be **used** *without* ***consideration*** of **clinical criteria**; A positive test may indicate the patient is a carrier for GABHS (not active infection), and the cause of pharyngitis could be viral.

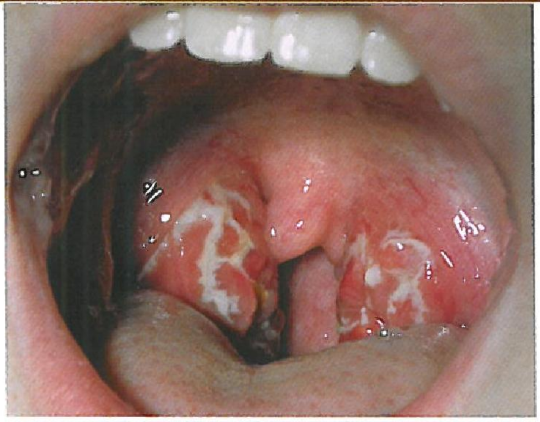
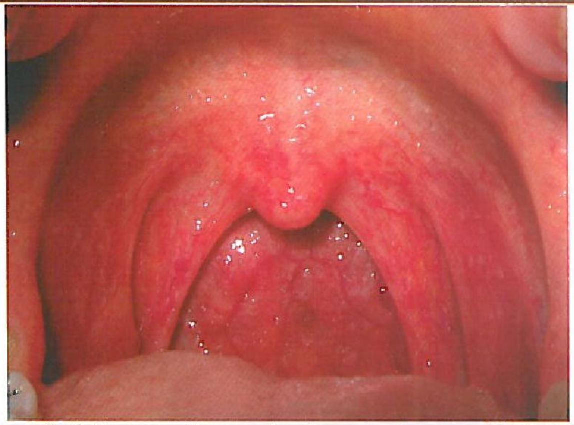
* **American Heart Association** (AHA), ***suggest*** that **testing** be ***done*** in ***all*** **patients** with **signs** and **symptoms** of **streptococcal pharyngitis**. *ONLY* those with a ***positive*** **test** for **GAS *require* antibiotic treatment.**

A) **Throat Culture**; is the ***gold*** **standard**; A throat swab can be sent for culture, but they require 24 to 48 hours for results.

B) **Rapid Antigen-Detection Test (RADT)**; More practical in that it provides results quickly, it can be performed at the bedside, and it is less expensive than culture.

* **American Heart Association** (AHA), ***recommends*** *follow-up* **throat cultures** for ***all*** **patients** *after* a ***negative*** **RADT** (*because* of the ***low*** **sensitivity** of *many* **RADTs**).

* **GAS *VS* Viral Pharyngitis**;

Features suggestive of GAS infection	Features suggestive of viral infection
	
Beefy, swollen, red uvula	Characteristic enanthems (rash on mucous membranes)
Fever	Characteristic exanthems (widespread rash)
Headache	Conjunctivitis
History of exposure to GAS	Coryza (Rhinitis)
Nausea, vomiting, and abdominal pain	Cough
Pain with swallowing	Diarrhea
Patient 5 to 15 years of age	Hoarseness
Presentation in winter or early spring (in temperate climates)	
Scarlet fever rash	
Soft palate petechiae (doughnut lesions)	
Sudden onset of sore throat	
Tender, enlarged anterior cervical nodes	
Tonsillopharyngeal erythema	
Tonsillopharyngeal exudates	

- Causes;
  - Rhinovirus; 20% of cases of pharyngitis.
  - Adenovirus; most commonly caused by adenovirus types 1-3 & 5
  - **Epstein-Barr Virus** (EBV) (**Mononucleosis** or **kissing Disease**); usually spreads from adults to infants. Among young adults, EBV spreads through saliva and, rarely, through blood transfusion. Pharyngitis or tonsillitis is present in about 82% of patients with infectious mononucleosis.
  - Other Viruses; Herpes simplex virus, Influenza virus and Coronavirus.

If clinical and epidemiologic findings suggest GAS infection, microbiologic confirmation with a throat culture or rapid antigen detection test (RADT) is required.

- **Pharmacotherapy** (***Recommendations***); **Acute Bacterial Pharyngitis**
  - *Primary* prevention of rheumatic fever requires ***adequate*** therapy for **GAS pharyngitis.**
  - ***Early*** initiation of antibiotic therapy ***results in*** faster resolution of signs and symptoms.
  - ***Delays*** in therapy (if ***awaiting*** cultures) can be *made* ***safely*** *for up to* **9 days *after* symptom onset** and *still* ***prevent major*** complications *such as* **rheumatic fever.**
  - **Patients** are ***no longer*** considered ***contagious*** *after* **24 hours** of **antibiotic therapy.**
  - *For over* **30 years, GAS *isolated*** in the **United States** has shown ***susceptibility*** to **Penicillin.**
  - **Treatment**;
    - **Pain Management** (**Paracetamol**, **NSAIDs**, **Lozenges** or **Sprays** containing menthol and topical anesthetics); for temporary relief of pain.
    - **Antibiotic therapy** (**Primary Prevention of Rheumatic Fever**)

Preferred Antibiotics			
	Adult Dosage	Pediatric Dosage	Duration
Amoxicillin	500 mg 3 times daily	40–50 mg/kg/day divided in 3 doses	10 days
Penicillin V	250 mg 3 or 4 times daily or 500 mg twice daily	50 mg/kg/day divided in 3 doses	10 days
Benzathine Penicillin	>27 kg; 1.2 million units IM	≤27 kg; 0.6 million units IM	Once
Additional Effective Antibiotics (*for patients allergic to penicillin*)			
Cephalexin	250–500 mg 4 times daily	25-50 mg/kg/day divided in 4 doses	10 days
Azithromycin	12 mg/kg once daily (maximum 500 mg)		5 days
Clarithromycin	15 mg/kg per day divided in 2 doses (maximum 250 mg twice daily)		10 days
Clindamycin	20 mg/kg per day divided into 3 doses (maximum 1.8 g/day)		10 days

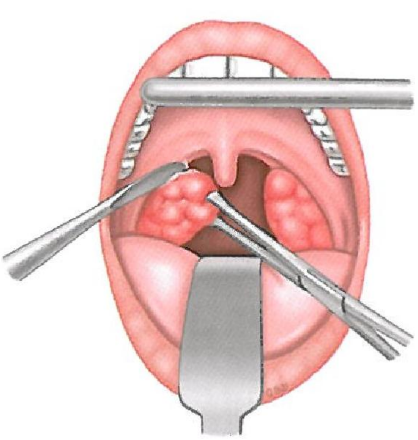
- **Secondary Prevention of Rheumatic Fever**;
  - **Duration of therapy**;

Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	10 years or until age 40 years (whichever is longer); lifetime prophylaxis may be needed
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	10 years or until age 21 years (whichever is longer)
Rheumatic fever without carditis	5 years or until age 21 years (whichever is longer)

  - **Antibiotic Therapy**;

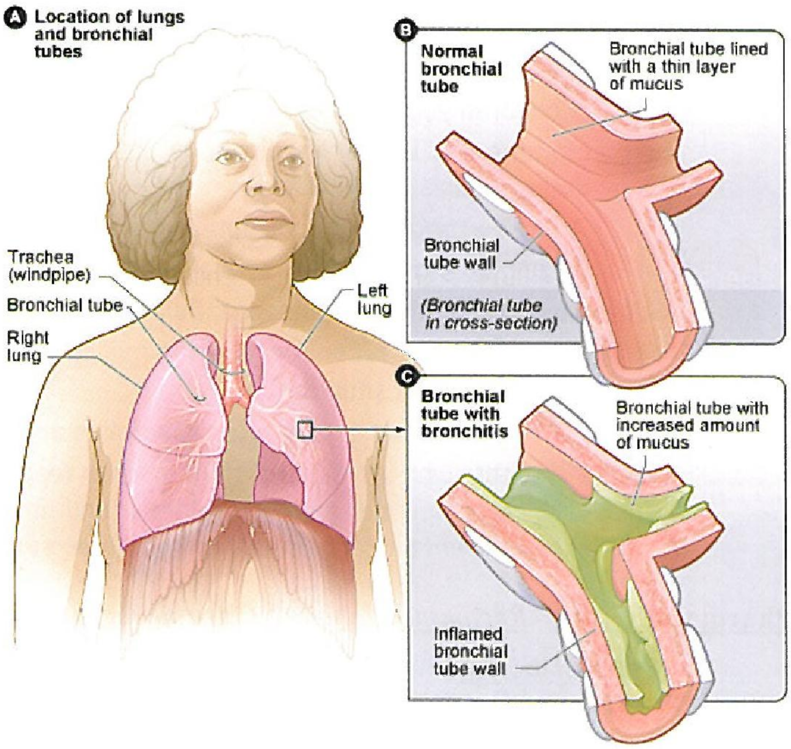
	Adult Dosage	Child Dosage
Preferred Antibiotics		
Benzathine Penicillin	>27 kg; 1.2 million units IM every 4 weeks	≤27 kg; 0.6 million units IM every 4 weeks
Penicillin V	250 mg orally twice daily	
For individuals allergic to Penicillin		
Sulfadiazine	1000 mg every 24 hours	500 mg every 24 hours
For individuals allergic to Sulfonamide or Penicillin		
Azithromycin	6 mg/kg every 24 hours	250 mg every 24 hours
Erythromycin	250 mg every 12 hours	

- **Tonsillectomy in Children Recommendations**;
  - **Watchful waiting** for ***recurrent*** **throat infection** is ***recommended*** if there have been ***fewer than* 7 episodes** in the **past year** OR ***fewer than* 5 episodes** *per* year in the *past* **2 years** OR ***fewer than* 3 episodes** *per year* in the *past* **3 years.**
  - **Tonsillectomy** may be *considered* for r ***recurrent* throat infection** with a *frequency* of ***at least* 7 episodes** in the *past* year OR ***at least* 5 episodes *per* year** for **2 years** OR ***at least* 3 episodes *per* year** for **3 years** with *documentation* in the **medical record** for ***each*** episode of sore throat and **1** or *more* of the following: **temperature > 38.3°C**, **cervical adenopathy**, **tonsillar exudate**, or *positive* test *for* **GAS**.



V) Bronchitis

- **Bronchitis** is an ***inflammation*** of the **bronchial tubes (bronchi)**, the **air *passages* that** *extend from* the **trachea** *into the **small*** **airways** and **alveoli**.
- **Bronchitis** is **one *of the* top conditions** for ***which*** **patients** *seek* **medical care**.
- **Bronchitis** *frequently* is ***classified as*** **acute** or **chronic**.
- **Acute bronchitis** occurs in *individuals* of ***all*** **ages**, *whereas* **chronic bronchitis** *primarily* affects **adults**.
- **Bronchiolitis** is a ***disease of*** **infancy**.
- **Acute bronchitis** usually has a **cough (hallmark)** that *lasts **around*** **3 weeks**. In ***more than*** **90%** of **cases** the cause is a **viral infection**.
- **Risk factors** include ***exposure*** to **tobacco smoke, dust**, and ***other*** **air pollution**.
- **Chronic bronchitis** is defined clinically as **cough *with* sputum *expectoration*** for ***at least*** **3 months** a **year *during a period*** of **2 consecutive years**.
- **Chronic bronchitis** is ***associated with*** **hypertrophy** of the **mucus-producing glands** found in the **mucosa** of **large cartilaginous *airways***.
- ***Most*** **people** with **chronic bronchitis** have **chronic obstructive pulmonary disease (COPD)**.


A Location of lungs and bronchial tubes
Trachea (windpipe)
Bronchial tube
Right lung
Left lung
B
Normal bronchial tube
Bronchial tube lined with a thin layer of mucus
Bronchial tube wall
(Bronchial tube in cross-section)
C
Bronchial tube with bronchitis
Bronchial tube with increased amount of mucus
Inflamed bronchial tube wall

- According to estimates from national interviews taken by the National Center for Health Statistics in 2006, approximately 9.5 million people, or 4% of the population, were diagnosed with chronic bronchitis.
- ***During*** an **episode** of **acute bronchitis**, the **cells** of the **bronchial-lining tissue** are ***irritated*** and the **mucous membrane** *becomes* **hyperemic** and **edematous**, ***diminishing*** **bronchial mucociliary *function***.
- **Causes**; *Approximately* **90%** of **acute bronchitis *infections*** are caused by **viruses**;
  - **Influenza virus**, **rhinovirus**, **coronavirus**, **respiratory syncytial virus** and **adenovirus**.
  - ***Mycoplasma*** **species**, ***Chlamydia pneumoniae***, ***Bordetella pertussis***, ***Streptococcus pneumoniae***, ***Moraxella catarrhalis*** and ***Haemophilus influenzae***.
  - **Exposure** to **irritants**; such as **pollution**, **chemicals**, and **tobacco smoke** (common causes in chronic bronchitis).
- **Diagnosis**; **Cough** is the ***most common*** **symptom**.
  - **Most Common Causes of Acute Cough**; Acute bronchitis, Allergic rhinitis, Asthma, Chronic obstructive pulmonary disease exacerbation, Common cold, Congestive heart failure exacerbation, Gastroesophageal reflux disease, Malignancy, Pneumonia, Postinfectious cough, Postnasal drip, Sinusitis, Viral syndrome and ACEIs antihypertensive agents.
    - **Coughing** with **nasal congestion** and **rhinorrhea**;
      - In **common cold**; *typically **lasts*** **only 7-10 days**.
      - In **acute bronchitis**; *typically **persist*** for approximately **3 weeks**.
  - **Pneumonia** can usually be ***ruled out*** in **patients *without*** **fever**, **tachypnea**, **tachycardia**, or **clinical lung findings** *suggestive of* **pneumonia** on ***examination***.
  - The ***presence*** or ***absence*** of **colored** (e.g., **green**) **sputum *does not*** reliably ***differentiate*** *between* ***bacterial*** and ***viral*** **lower respiratory tract infections**.
  - ***Bordetella pertussis*** (whooping cough); **cough** has a "**whooping**" **sound**.

- **Pharmacotherapy** (***Recommendations***); **Acute Bronchitis;**
  - *In general*; **treatment** of **acute bronchitis** is **symptomatic** and **supportive** in ***nature***.
    - Antipyretics as needed.
    - Bed rest for comfort.
    - Encouraged to drink fluids.
    - Mist therapy (use of a vaporizer).
  - ***Mild*** **analgesic–antipyretic therapy** can be *helpful* in ***relieving***; **lethargy**, **malaise** and **fever**.
  - **Cough suppressants**; such as **Codeine** and **Dextromethorphan** are ***recommended for*** *short-term* **symptomatic relief** of **coughing**.
    - * **American Academy** of **Pediatrics** and the **FDA** to ***recommend*** *against* the use of **antitussive medications** in **children** ***younger than*** **2 years**.
    - * **FDA** ***subsequently*** **recommended** that **cough** and **cold preparations** *not be* **used** in **children** ***younger than*** **6 years**.
  - **Expectorants** and **inhaler medications** are ***not recommended*** for *routine* use in **patients** *with* **bronchitis**; *Patients with* **wheezing**;
    - * ***Short-acting*** **β_2 agonists**, **Ipratropium** and **Theophylline** can be used.
    - * ***Long-acting*** **β_2 agonist** + ***Inhaled*** **corticosteroid**, can be offered to ***control*** **chronic cough**.
  - **Alternative medications**; **Echinacea**, **Pelargonium** and **Honey** have ***benefits*** in **bronchitis**.
  - **Antibiotics**; are ***not recommended*** for *routine* use in **patients** with **bronchitis**, they may be ***considered*** in **certain situations**.
    - * When **pertussis** is ***suspected***; **Macrolide antibiotic** is ***recommended***.
    - * **Patients** who *exhibit* ***persistent*** **fever** or **respiratory symptoms** for *more than* **4-6 days** or for **predisposed patients** (**elderly** and **immunocompromised**), the ***possibility*** of a ***concurrent*** **bacterial infection** ***should be*** **suspected**.

- **Pharmacotherapy** (***Recommendations***); **Chronic Bronchitis;**
  - **Goals of therapy**;
    - * ***Reduce*** the **severity** of **chronic symptoms**.
    - * ***Ameliorate*** **acute exacerbations**.
    - * ***Achieve*** **prolonged infection-*free* intervals**.
  - **Reduce** the **patient's exposure** to **bronchial irritants**; such as **smoking** and **workplace** ***pollution***.
    - * **Smoking Cessation Program**, including ***counseling*** and ***hypnotherapy***, the ***adjunctive*** use of **nicotine substitutes** (e.g., **nicotine gum** or **patch**) or ***other*** **pharmacotherapy** (e.g. **Varenicline** or **Bupropion**) may ***promote*** the *reduction* or *complete* ***withdrawal from*** **cigarette smoking**.
  - **Reduce Mucus Production**;
    - * **Smoking cessation** and **avoidance** of **environmental irritants**; ***decrease*** **goblet cell** ***stimulation*** and ***hyperplasia***.
    - * **Anticholinergics**; ***decrease*** **mucus secretion**.
    - * **Inhaled glucocorticoids**; ***reduce*** **inflammation** and thus **mucus** ***production***.
    - * **PDE-4 inhibitors** (**Roflumilast**); may ***decrease*** **COPD exacerbations** in *patients with* ***concomitant*** **chronic bronchitis**; by ***decreasing*** **mucus secretions**.
  - **Facilitate Mucus Elimination**;
    - * **Methylxanthines** and ***short-acting*** **β_2-agonists** via ***increase*** **airway lumen diameter**.
    - * ***Inhale*** **hypertonic saline**; ***directly*** **rehydrate airways** and ***promotes*** **cough** (minimal evidence to show benefit).
    - * **Physical maneuvers** such as **chest physical therapy** or **flutter valve** *may help* to ***augment*** **shear stressors** to ***aid*** **mucus breakdown** and **clearance** (minimal evidence available).
    - * **Expectorants** (**Guaifenesin**) **vagally medicate** *increase* in **airway secretions** ***improving*** **mucus clearance** in the ***short term*** (no long-term benefit found).

- **Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB);**
  - **3 clinical factors** are ***considered***: **Dyspnea**, **Sputum Volume** and **Sputum Purulence**:
    - * ***Change*** in **sputum color** has also been *recognized to* be a **strong *predictor*** of ***presence*** of ***potentially*** **pathologic microorganisms** in **ABECB**.
  - **Antibiotic** is ***recommended for*** **Moderate** (2 of 3 symptoms) **Exacerbations**,
    OR **Severe** (all 3 symptoms) **Exacerbations**.

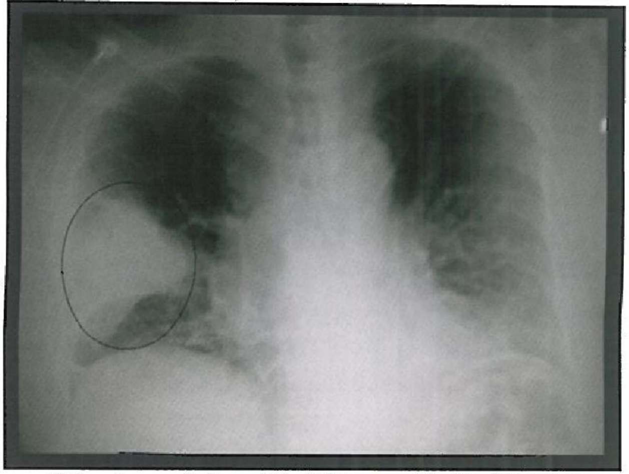
- **Mild ABECB**:
  - ***No* antibiotics** *recommended.*
  - ***Outpatient*** **symptomatic therapy** and ***monitor*** for ***worsening*** **symptoms**.

- **Moderate ABECB**; and/or any one of the following: age < 65 years, FEV1 >50% predicted, no cardiac disease, or < 3 exacerbations per year:
  - **Azithromycin** 500 mg orally on first day then 250 mg daily for next 4 days OR
  - **Clarithromycin** 250-500 mg orally every 12 hours for 7-14 days OR
  - **Doxycycline** 100 mg orally every 12 hours for 7 days OR
  - **Trimethoprim-sulfamethoxazole** (160 mg/800 mg) 1 DS tablet twice for 10-14 days OR
  - **Cefuroxime** 250-500 mg orally every 12 hours for 10 days OR
  - **Cefdinir** 300 mg orally every 12 hours for 5-10 days OR
  - **Cefpodoxime** 200 mg orally every 12 hours for 10 days.
  - * If recent antibiotic exposure within 3 months, use alternative class.

- **Severe ABECB**; and/or anyone of the following: age ≥65 years, FEV1 ≤ 50% predicted, cardiac disease, or ≥3 exacerbations per year:
  - * Consider hospitalization.
  - Amoxicillin/Clavulanate (875 mg/125 mg) 1 tablet every 12 hrs for 7-10 days OR
  - Levofloxacin 750mg orally daily for at least 7 days OR
  - Gemifloxacin 320mg orally daily for 5 days OR
  - Moxifloxacin 400 mg orally daily for 5 days.
  - * If at risk for *Pseudomonas* infection consider sputum culture and treatment with Levofloxacin 750 mg orally daily for 14 days.
  - * If recent antibiotic exposure within 3 months, use alternative class.

VI) Pneumonia

- **Pneumonia** is an **inflammatory condition** of the **lung** *affecting primarily* in **alveoli.**
- **Pneumonia** ***affects*** *approximately* **450 million people** ***globally*** (7% of the population) and ***results in*** *about* **4 million deaths** *per* **year.**
- **Pneumonia** is the ***most common*** cause of **death** *attributable to* **infectious diseases** (***very high rates*** in **older adults**) and in the **top 10** *causes* of **death** in the **United States.**



- **Causes**; ***usually*** by **infection** *with* **viruses** or **bacteria** and ***less commonly*** by *other* **microorganisms**, *certain* **medications** and **conditions** such as **autoimmune diseases.**
- **Risk factors**; **cystic fibrosis, COPD, asthma, diabetes, heart failure**, a *history of* **smoking** and **weak immune system.**
- **Symptoms** ***occur*** as a *result of* **oxygen-absorbing areas** of the **lung (alveoli)** ***filling*** with **fluid.** This ***inhibits*** **lung function**, causing **dyspnea, fever, chest pains** and **cough.**

Community-Acquired Pneumonia (CAP)

- **Community-Acquired Pneumonia** (**CAP**) is **one** of the ***most common*** **infectious diseases** and is an ***important cause*** of **mortality** and **morbidity** ***worldwide.***
- **CAP** is ***acquired*** in the **community**, ***outside*** of **health care facilities** (no contact to a medical facility).
- **Patients** ***must*** also **NOT** *have* ***any*** of the ***following characteristics***:
    * **Hospitalization 2 days** or **more** in the ***past*** **90 days.**
    * **Residence** in a ***long-term*** **care facility.**
    * **Receipt** of ***intravenous*** **antibiotic therapy, chemotherapy**, or **wound care** in the ***past*** **30 days.**
    * **Attendance** at a **hospital** or **hemodialysis clinic.**
- **Symptoms** of **CAP**;
    * **Fever** or **hypothermia.**
    * **Sweats.**
    * **Chest discomfort.**
    * **Rigors** (**tremor** *caused by* a **chill**).
    * ***New*** **onset** of **cough** ***with*** or ***without*** **sputum.**
    * **Onset** of **dyspnea.**
    * **Fatigue, myalgias, abdominal pain, anorexia**, and **headache.**
- ***Most common*** **etiologies** of **CAP**; ***Streptococcus pneumoniae*** *remains* the ***most common***;
    * ***Streptococcus pneumoniae***
    * ***Chlamydophila pneumoniae***
    * ***Mycoplasma pneumoniae***
    * ***Legionella pneumophila***
    * ***Haemophilus influenzae***
    * **Respiratory viruses**
- **Diagnosis**; ***based on***;
    1) ***Presence*** of ***select*** **clinical features** (**fever**, ***new onset*** of **cough +/- sputum** and **pleuritic chest pain**).
    2) ***Supported by*** **imaging** of the **lung**, usually by **chest radiography.**
    3) **Physical examination** to ***detect*** **rales** or **bronchial breath sounds.**
- **CURB-65 criteria** (**C**onfusion, **U**remia, **R**espiratory rate, low **B**lood pressure, age **65** years or greater); used to predictors severity-of-illness scores;

CURB-65	
Symptom	**Points**
Confusion	1
Urea >19 mg/dL	1
Respiratory rate ≥30 breaths/minute	1
SBP <90 mm Hg, DBP ≤60 mm Hg	1
Age ≥65 years	1

DBP = diastolic blood pressure; SBP = systolic blood pressure; ICU = Intensive Care Unit

* **CURB-65 Location of Therapy**;

Score	Risk of Death at 30 Days (%)	Location of Therapy
0	0.7	Treat as outpatient
1	2.1	Treat as outpatient
2	9.2	Outpatient or inpatient
3	14.5	Inpatient (±ICU)
4	40.0	Inpatient (±ICU)
5	57.0	Inpatient (±ICU)

- **Pharmacotherapy** (***Recommendations***); **Community-Acquired Pneumonia (CAP)**;

Empirical Antibiotic Therapy	
Non-hospitalized patients (**Outpatient**)	
***Previously* healthy and *NO* antibiotic therapy in the *past* 3 months**	* **Macrolide** (**Clarithromycin** or **Azithromycin** if *Haemophilus influenzae* is suspected) OR * **Doxycycline**
Comorbidities (COPD, diabetes mellitus, chronic renal or liver failure, congestive heart failure, malignancy, asplenia, or immunosuppression) OR **recent antibiotic therapy** (within ***past* 3 months**)	* **Respiratory Fluoroquinolone** (**Moxifloxacin**, **Gemifloxacin**, or **Levofloxacin** 750 mg) OR * **Macrolide** (OR **Doxycycline**) PLUS *high-dose* **Amoxicillin** (1 g 3 times/day) or **Amoxicillin/Clavulanate** (2 g twice daily) or a **Cephalosporin** (**Ceftriaxone**, **Cefuroxime** or **Cefpodoxime**)
Hospitalized patients (**Inpatient**)	
***Moderately severe* pneumonia** (Non- ICU)	* **Respiratory Fluoroquinolone** (**Moxifloxacin**, **Gemifloxacin**, or **Levofloxacin** 750 mg) OR * **Ampicillin** (OR **Ceftriaxone**, OR **Cefotaxime** (**Ertapenem** in select patients) PLUS **Macrolide** (OR **Doxycycline**).
***Severe* pneumonia** (ICU) (may need to add other antibiotics if *P. aeruginosa* or MRSA is suspected)	* **Ampicillin/Sulbactam** (OR **Ceftriaxone** OR **Cefotaxime**) PLUS **Respiratory Fluoroquinolone** (OR **Azithromycin**).

* **Treatment Duration**; ***At least* 5 days**, *with* **48–72 hours *afebrile*** (***without* fever**; **feverless**) and ***NO more than* one sign** of **clinical instability** (elevated temperature, heart rate, or respiratory rate; decreased systolic blood pressure; or arterial oxygen saturation) ***before* therapy discontinuation**.

* **Special Considerations**;

A) **Risk factors** for ***Pseudomonas* species**;

* **β-lactam antibiotic** (**Piperacillin/Tazobactam**, **Cefepime**, **Imipenem/cilastatin**, **Meropenem**, or **Doripenem**) PLUS **Ciprofloxacin** OR **Levofloxacin**. OR
* The *above* **beta-lactam antibiotic** PLUS an **Aminoglycoside** and **Azithromycin** OR
* The *above* **beta-lactam antibiotic** PLUS an **Aminoglycoside** and an ***anti-pneumococcal* respiratory fluoroquinolone** (**Moxifloxacin**, **Gemifloxacin**, or **Levofloxacin** 750 mg)

B) **Risk factors** for **methicillin-resistant *Staphylococcus aureus*** (**MRSA**); add **Vancomycin** OR **Linezolid**

C) **Influenza virus**; **Oseltamivir** OR **Zanamivir**.

Nosocomial Pneumonia

- **Nosocomial Pneumonia** or **Hospital-acquired pneumonia** (**HAP**) *refers to any* **pneumonia** ***contracted by*** a **patient** *in* a **hospital**.
  * **HAP** is the ***second* most common *nosocomial infection*** (*after* **urinary tract infections**) and ***accounts* for 15–20%** of the ***total***.
  * It is the ***most common*** cause of **death** among ***nosocomial* infections**.
  * It is the ***primary*** cause of **death** in **intensive care units**.
- ***Types***;

A) **Hospital-Acquired Pneumonia** (**HAP**); **Pneumonia** that ***occurs* 48 hours** or ***more after* admission** and was ***not incubating*** at the **time** *of* **admission** (***higher risk*** of **multidrug-resistant pathogens**).

B) **Health Care-Associated Pneumonia** (**HCAP**); **Pneumonia** ***developing*** in a **patient** ***who***;

* Was ***hospitalized* 2 days** or ***more*** in the ***past* 90 days**.
* Was ***resided*** in a **nursing home** or ***long-term* care facility**.
* Was ***received*** **IV antibiotic therapy**, **IV chemotherapy**, or **wound care** in the ***past* 30 days**.
* Was ***attended*** a **hospital** or **hemodialysis clinic**.

C) **Ventilator-Associated Pneumonia** (**VAP**); **Pneumonia** that **arises *more than* 48–72 hours *after* endotracheal intubation**.

- ***Risk Factors*** for **Nosocomial Pneumonia**;
    - Intubation and mechanical ventilation
    - Supine patient position
    - Enteral feeding
    - Oropharyngeal colonization
    - Stress bleeding prophylaxis
    - Blood transfusion
    - Hyperglycemia
    - Immunosuppression or corticosteroids
    - Surgical procedures: upper abdominal and thoracic
    - Immobilization
    - Nasogastric tubes
    - Previous antibiotic therapy
    - Admission to the intensive care unit
    - Advanced age
    - Underlying chronic lung disease

- ***Most common*** **etiologies** of **HAP**; ***Staphylococcus aureus*** remains the ***most common***;
    - * ***Staphylococcus aureus***
    - * ***Pseudomonas aeruginosa***
    - * ***Klebsiella pneumoniae***
    - * ***Escherichia coli***
    - * ***Acinetobacter* spp.**

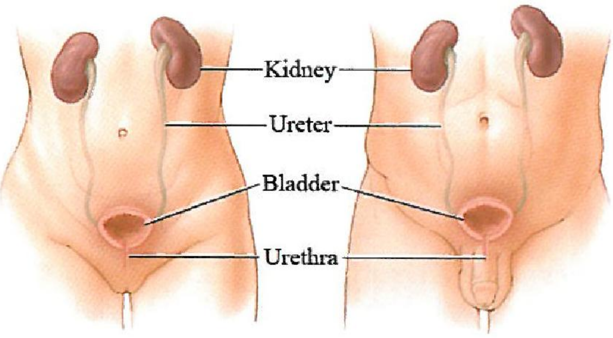
- **Pharmacotherapy** (***Recommendations***); **Hospital Acquired**, **Ventilator Associated**, or **Healthcare Associated Pneumonia**;

No* risk factors for multidrug-resistant (MDR) *pathogens	*S. pneumoniae*, *H. influenzae*, MSSA, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp. and *Proteus* spp.	**Ceftriaxone** OR **Fluoroquinolone (Levofloxacin, Moxifloxacin** or **Ciprofloxacin)** OR **Ampicillin/Sulbactam** OR **Ertapenem** OR **Doripenem**
***Risk factors* for MDR pathogen**	*Pseudomonas aeruginosa*, *Klebsiella pneumoniae* (ESBL; Extended-spectrum β-lactamase), *Acinetobacter* spp., MRSA, and *Legionella pneumophila*	* **Antipseudomonal Cephalosporin (Ceftazidime** or **Cefepime)** OR **Imipenem, Meropenem**, or **Doripenem** OR **Piperacillin/Tazobactam** PLUS **Aminoglycoside** OR **Fluoroquinolone (Ciprofloxacin, Levofloxacin)** * **Vancomycin** or **Linezolid** should be added to the above regimens only if MRSA risk factors

- **Treatment duration**; **Efforts *should be*** made to ***decrease*** **therapy duration** to ***as short as*** **7** or **8 days** (**14 days** for **pneumonia** *secondary to* ***P. aeruginosa*** or ***Acinetobacter***).

- **Risk Factors for MDR Pathogens**;
    - * **Antibiotic therapy** *within* the ***past*** **90 days**.
    - * **Hospitalization** of **5 days** or ***more***.
    - * ***High resistance*** in **community** or **hospital unit**.
    - * **Risk factors** for **health care-associated pneumonia**;
        - **Hospitalization** for **2** or ***more*** **days** in the ***preceding*** **90 days**.
        - **Residence** in a **nursing home** or ***extended*** **care facility**.
        - **IV therapy** (*including* **antibiotics**) or **IV chemotherapy** ***within*** **30 days**.
        - ***Attendance*** at a **hospital** or **hemodialysis clinic**.
        - **Home wound care** ***within*** **30 days**.
    - * **Family member** *with* **MDR pathogen**.
    - * **Immunosuppressive *disease*** or ***therapy***.

B) Urinary Tract Infections (UTIs)



- **Urinary Tract Infection** (**UTI**); is an ***infection*** that ***affects*** **part** *of* the **urinary tract**;
  - ***Lower* Urinary Tract Infection**; it is known as a **bladder infection** (**cystitis**).
  - ***Upper* Urinary Tract Infection**; it is known as **kidney infection** (**pyelonephritis**).
- **UTIs** are ***classified as*** **uncomplicated** and **complicated**;
  - **Uncomplicated** *refers to* an **infection** *without* **structural** or **functional** ***abnormalities*** of the **urinary tract**.
  - **Complicated** are usually *associated with* a ***predisposing*** **lesion** of the **urinary tract**;
    - **Metabolic Factors**; Renal failure, diabetes mellitus and kidney transplantation.
    - **Functional Abnormalities**; Neurologic abnormalities in bladder.
    - **Structural Abnormalities**; Congenital abnormalities, distortion of the UT, stones, obstruction and prostatic hypertrophy.
  - **Factors *associated with*** or ***used to*** define **complicated UTI**;
    - Male sex
    - Pregnancy
    - Diabetes mellitus
    - Hospital acquired infection
    - Anatomic abnormality of the urinary tract
    - Childhood UTIs
    - Recent antimicrobial use
    - Indwelling urinary catheter
    - Recent urinary tract instrumentation
    - Immunosuppression

- ***Recurrent* UTIs** are considered *either* ***reinfections*** or ***relapses***;
  - **Reinfection** *usually happens* ***more than* 2 weeks *after*** the ***last*** **UTI**, and is ***treated as*** a **new *uncomplicated*** **UTI**.
  - **Relapse** *usually happens* ***within* 2 weeks** of the ***original*** **infection** and is a ***relapse*** of the **original infection** either *because* of ***unsuccessful*** **treatment** of the **original infection**, a ***resistant*** **organism**, or **anatomical *abnormalities***.
- **UTIs** are the ***most common*** **bacterial infection** in **humans**; in the **United States**, these infections account for *approximately* **7 million *office visits*** and ***more than* 1 million *hospitalizations*** *per* **year**, and *overall* ***annual cost*** in *excess of* **$1 billion**.
- The ***most common*** **cause** of ***infection*** is ***Escherichia coli***.
- ***Incidence*** of **UTIs** by **organism**;

Community Acquired		Nosocomial	
Escherichia coli	73%	*Escherichia coli*	31%
Staphylococcus saprophyticus	13%	*Pseudomonas aeruginosa*	10%
Proteus mirabilis	5%	Other gram-negative bacilli	10%
Klebsiella pneumoniae	4%	*Klebsiella pneumoniae*	9%
Enterococcus	2%	*Staphylococcus aureus*	6%
		Proteus mirabilis	5%
		Enterococcus	2%
		Fungal	14%

- ***Predisposing Factors***;
  - Age
  - Pregnancy
  - Urinary tract obstruction
  - Female sex
  - Immunosuppression
  - Renal disease; renal transplantation
  - Diabetes mellitus
  - Urinary tract instrumentation
  - Neurologic dysfunction

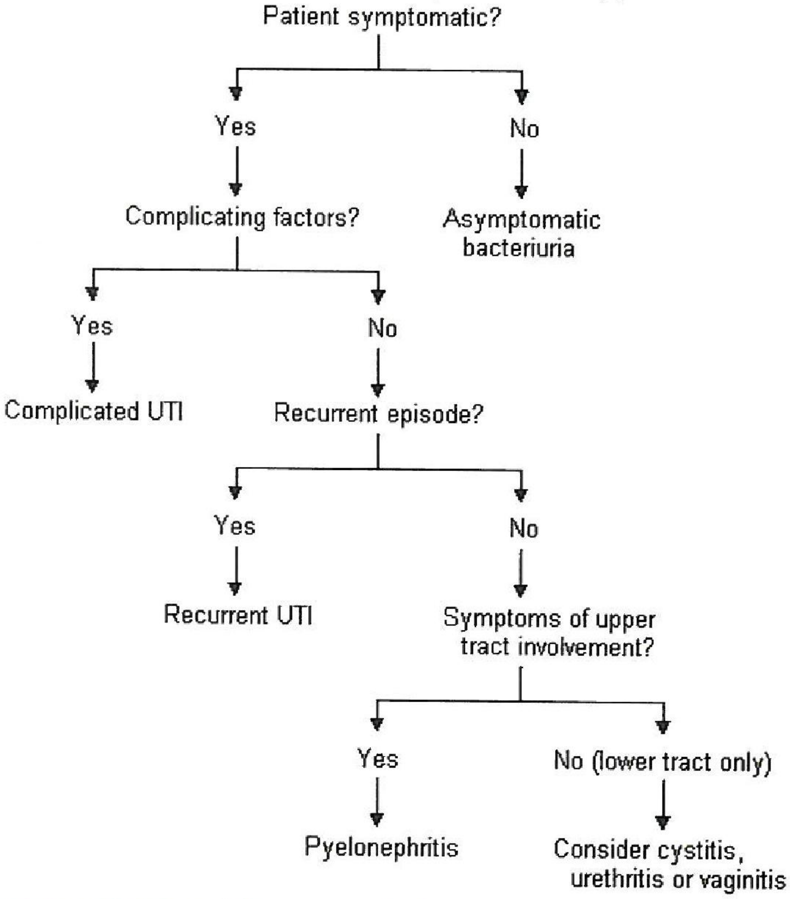
- *Symptoms*;

Lower UTI (Cystitis)	Upper UTI (Pyelonephritis)
Dysuria	Frequency, dysuria, haematuria
Frequent urination	Suprapubic pain
Urgency	Costovertebral angle tenderness; **flank pain**
Occasionally, gross haematuria	**Fever**, chills
Occasionally, foul-smelling urine	Elevated WBC
	Nausea, vomiting

* **Older adults**; may have only nonspecific symptoms, such as mental status changes, abdominal pain, and decreased eating or drinking.

- ***Diagnosis*; Urinalysis**
  - Pyuria (urine containing white blood cells or pus); WBC > 5–10 cells/mm^3.
  - Bacteriuria; > 102 colony-forming units per millilitre is diagnostic.
  - Red blood cells.
  - Cloudiness.
  - Nitrite positive.
  - Leukocyte esterase positive.
  - Casts (if pyelonephritis).

* Blood cultures will be positive in 20% of patients with upper UTIs.


Patient symptomatic?
Yes
No
Complicating factors?
Asymptomatic bacteriuria
Yes
No
Complicated UTI
Recurrent episode?
Yes
No
Recurrent UTI
Symptoms of upper tract involvement?
Yes
No (lower tract only)
Pyelonephritis
Consider cystitis, urethritis or vaginitis

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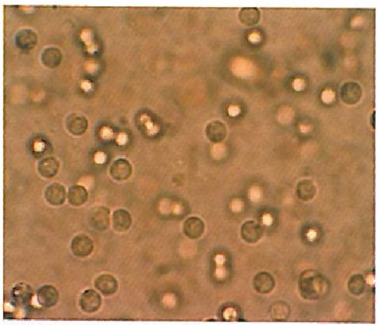
Pyuria and Cloudiness



White blood cells seen under a microscope from a urine sample

- **Pharmacotherapy** (***Recommendations***);
  - **1) Uncomplicated Cystitis;**
    - * * **Recommended therapy;**
      - **Trimethoprim/Sulfamethoxazole 160mg/800mg *twice* daily *for* 3 days** (***Avoid*** if **resistance *prevalence*** is known to ***exceed*** 20% OR if **used** for **UTI** in *previous* **3 months**).
      - **Nitrofurantoin 100 mg *twice* daily *for* 5 days.**
      - **Fosfomycin 3 g, one dose.**
    - * **Alternatives;**
      - **Fluoroquinolones** *for* **3 days.**
      - **β-Lactams** *for* **3–7 days.**

2) **Uncomplicated pyelonephritis**;
- * **Outpatient therapy** (if patient is ***not* immunocompromised** or does ***not*** have **nausea and vomiting**);
  - **Trimethoprim/Sulfamethoxazole** *for* **14 days.**
  - **Fluoroquinolones** *for* **5–7 days.**
  - **β-Lactams** *for* **10–14 days** (less effective than first two options).
- * **Uropathogen resistance** (***greater than*** 10%);
  - **Use *initial* dose** of an **intravenous;**
    - ***Long-acting* β-lactams** (e.g., **Ceftriaxone**).
    - ***Once-daily* Aminoglycosides.**

3) **Complicated UTIs**;
- * **Inpatient therapy**; **Fluoroquinolones**, **Aminoglycosides** OR ***Extended-spectrum* β-lactams**; **therapy duration**: **5–14 days (5 days *with* Levofloxacin).**

4) **UTIs** in **Pregnancy** (pregnant women should be screened for bacteriuria and treated, even if asymptomatic)
- * **7-day treatment regimen**;
  - **Amoxicillin.**
  - **Nitrofurantoin** (***avoid after* 38 weeks' gestation** and ***during* labor** and **delivery**).
  - **Cephalexin.**
- * **Antibiotics to avoid**; **Fluoroquinolones**, **Tetracyclines**, **Aminoglycosides** and **Trimethoprim/Sulfamethoxazole** (used frequently but avoidance recommended, especially during the late third trimester).

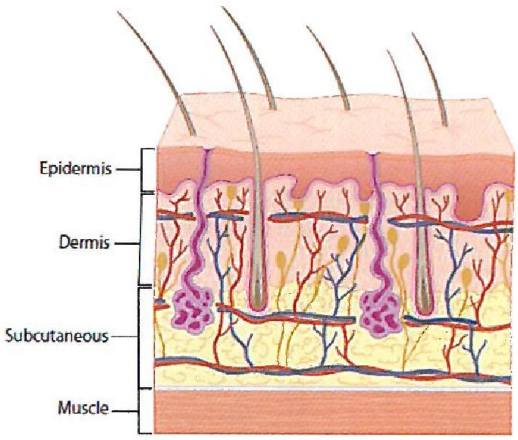
5) **Recurrent cystitis**;
- * **Relapse**;
  - *Assess* for **pharmacologic reason** *for* **treatment failure.**
  - ***Longer* treatment** (for 2–6 weeks, depending on length of initial course).
- * **Reinfection** (***re-assess*** need for ***continuous* prophylactic antibiotics** *every* **6–12 months**);
  - *If patient* has **2** or ***fewer* UTIs** in **1 year**;
    - Use therapy for **symptomatic** episodes (3-day treatment regimens).
  - *If patient* has **3** or ***more* UTIs** in **1 year** and are temporally ***related to* sexual activity**;
    - Use ***post-intercourse* prophylaxis** with **Trimethoprim/Sulfamethoxazole *single* strength**, **Cephalexin 250 mg** OR **Nitrofurantoin 50–100 mg.**
  - *If patient* has **3** or ***more* UTIs** in **1 year** that are ***not related*** to **sexual activity**;
    - Use ***daily*** or ***three* times** *per* **week *prophylaxis*** with **Trimethoprim 100 mg**, **Trimethoprim/Sulfamethoxazole *single* strength**, **Cephalexin 250 mg** OR **Nitrofurantoin 50–100 mg.**

6) **Catheter-related UTIs**;
- * **Short-term indwelling catheters**;
  - *About* **5%** of **patients** *develop* a **UTI** *per* ***each* day** of **catheterization**; by **30 days**, **75%–95%** of **patients** with an ***indwelling* catheter** will have **bacteriuria**.
  - The ***most common* organisms** are *Escherichia coli* (21.4%), *Candida* spp. (21.0%), *Enterococcus* spp. (14.9%), *Pseudomonas aeruginosa* (10.0%), *Klebsiella pneumoniae* (7.7%), and *Enterobacter* spp. (4.1%).
  - ***Preventive* antimicrobial therapy** is ***not recommended***; it **only *increases*** the **chance** of *selecting out* **resistant organisms**.
  - **Asymptomatic patients** with **bacteriuria *should not*** be **treated**.
  - **Symptomatic patients** with **bacteriuria *should be*** **treated** *with*;
    - **7 days** of **antibiotics** *if* **symptoms *resolve* promptly**.
    - **10–14 days** of **antibiotics** *if* there is a ***delayed* response**.
    - **5 days** with **Levofloxacin** if the patient is ***not severely* ill**.
    - **3 days** with **Levofloxacin** in **women 65 years** and ***younger*** who have their **catheters *removed*** and who ***do not*** have **upper urinary tract *symptoms***.
- * **Long-term indwelling catheters**;
  - **Almost *all* patients** will be **bacteriuric** with **2** to **5 organisms**.
  - ***Asymptomatic* patients** *should not* be **treated**.
  - ***Symptomatic* patients** *should* be **treated** for a ***short period*** (**7 days**) to ***prevent* resistance**, and **catheter *replacement*** may be ***indicated***.

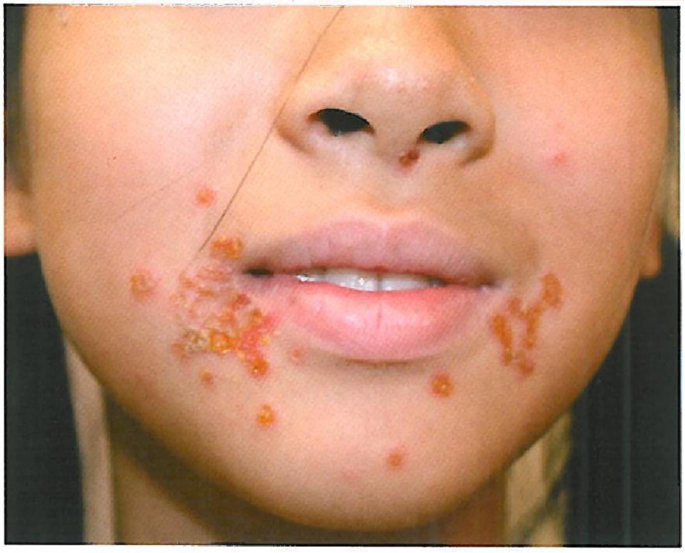
Prostatitis was discussed previously in; Urinary Tract System Chapter

C) Skin and Soft-Tissue Infections (SSTIs)

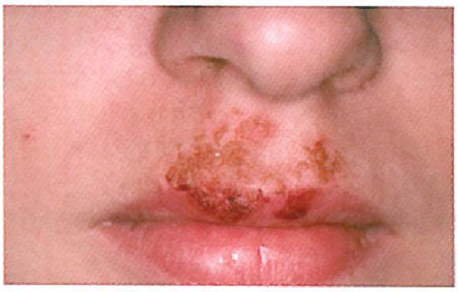
- **Skin** and **soft-tissue infections** (**SSTIs**), which ***include*** **infections** of **skin**, **subcutaneous tissue**, **fascia**, and **muscle**.
- The ***various*** **types** of **SSTIs**, *include the following*;
  - **Impetigo** (Highly contagious bacterial skin infection).
  - **Folliculitis** (Infections of hair follicles).
  - **Furuncles** (Boils of bacterial infections).
  - **Carbuncles** (Cluster of furuncles).
  - **Cellulitis** (Noncontagious bacterial skin infection).
  - **Erysipelas** (Bacterial infection in the upper layer of the skin).
  - **Necrotizing fasciitis** (Flesh-eating disease).
  - **Pyomyositis** (Bacterial infection of the skeletal muscles).
- ***Most important*** **pathogens** in **SSTIs** are ***Staphylococcus aureus*** (most common) and ***Streptococcus pyogenes*** (**Group A *streptococci***).



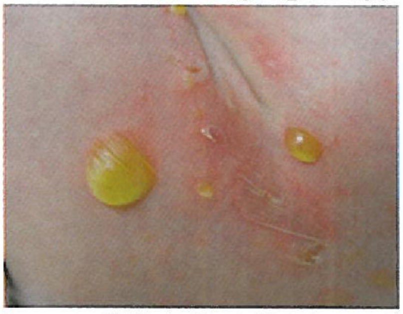
I) Impetigo



- **Impetigo** is a ***highly contagious superficial*** **skin infection.**
- It is the ***most common*** **bacterial infection** in **children**.
- It is *characterized by* **fluid-filled vesicles** that ***develop rapidly*** into **pus-filled blisters** that ***rupture*** to ***form*** **golden-yellow crusts**.
- **Impetigo** is usually **diagnosed *based on*** its ***appearance*** → → → → → → → → → → →
- **Common pathogens**; ***Streptococcus pyogenes*** and ***Staphylococcus aureus***.
- **Impetigo *affected*** *about* **140 million people** (**2%** of the **world population**) in **2010**.
- **Impetigo** is generally ***classified as*** **bullous** or **non-bullous** based on **clinical presentation.**
- **Bullous Impetigo** form affect *about* **10%** of ***all*** **cases** of **impetigo** (affects **neonates *most frequently***)
- The **bullous *form*** is caused by **strains** of ***Staphylococcus aureus*** *capable of* ***producing*** **exfoliative toxins**.
- **Impetigo** *may* **resolve *spontaneously***, **treatments *relieve*** **symptoms**, ***prevent formation*** of **new lesions**, and ***prevent*** **complications** such as **cellulitis**.



Non-bullous Impetigo



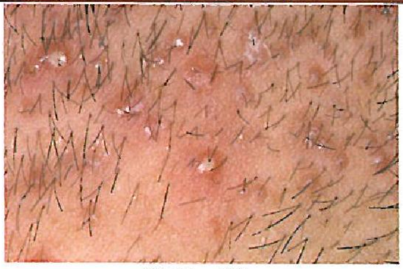
Bullous Impetigo

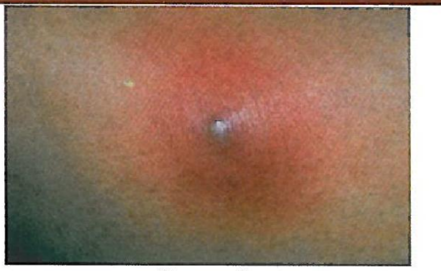
- **Pharmacotherapy** (***Recommendations***);

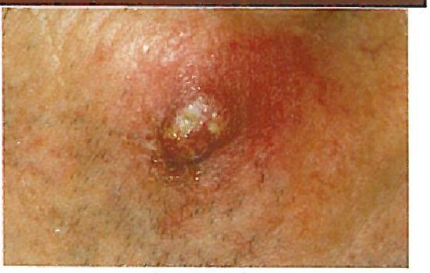
Antibiotic	Adult Dose	Child Dose
Dicloxacillin	250 mg orally 4 times daily	Not Applicable (N/A)
Cephalexin	250 mg orally 4 times daily	25–50 mg/kg/d in 3–4 divided doses
Erythromycin	250 mg orally 4 times daily	40 mg/kg/d in 3–4 divided doses
Clindamycin	300–400 mg orally 4 times daily	20 mg/kg/d in 3 divided doses
Amoxicillin-Clavulanate	1 gm (875/125) orally twice daily	25 mg/kg/d of the amoxicillin in 2 divided doses

- For patients with ***limited*** **number** of **lesions**;
  - **Retapamulin** *ointment* apply to lesions twice daily.
  - **Mupirocin** *ointment* apply to lesions twice daily.

II) Folliculitis, Furuncles and Carbuncles


Folliculitis
(Infections of hair follicles)


Furuncle
(Boil of bacterial infection)

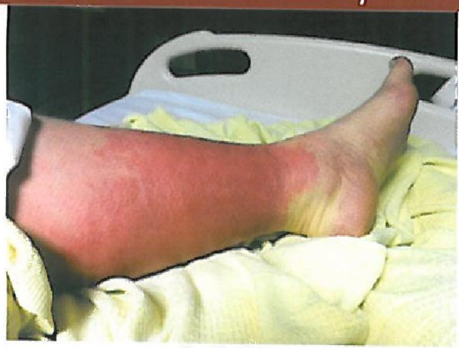

Carbuncle
(Cluster of furuncles)

- **Folliculitis** is ***inflammation*** of the **hair follicle** and is *caused by* **physical injury**, **chemical irritation**, or **infection**.
- **Folliculitis** is a ***superficial*** **infection** with **pus** ***present only*** in the **dermis**.
- **Furuncles** (**boils**) and **Carbuncles** occur when a **follicular infection** ***extends*** *from* **around** the **hair shaft** *to* **involve** ***deeper areas*** of the **skin**.
- The ***lesions*** of **furuncles** are *called* **Carbuncles** when they **coalesce** and ***extend*** to the **subcutaneous tissue**.
- **Folliculitis**, **Furuncles**, and **Carbuncles** are caused most often by ***Staphylococcus aureus***.
- **Pharmacotherapy** (***Recommendations***);
  - * ***Treatment of*** **Folliculitis** *generally* **requires ONLY** ***local*** **measures**; such as **warm moist compresses** or **topical therapy** (e.g., **Clindamycin**, **Erythromycin**, **Mupirocin**, or **Benzoyl peroxide**); **Topical agents** *generally* are *applied* **2** to **4** ***times*** **daily** for **7 days**.
  - * ***Small*** **Furuncles** *generally* can be **treated** with **moist heat**, which ***promotes*** **localization** and **drainage** of **pus**.
  - * ***Large*** and/or ***multiple*** **Furuncles** and **Carbuncles** *require* **incision** and **drainage**.
  - * **Systemic antibiotics**; are ***usually*** **NOT** ***necessary*** *unless* ***accompanied by*** **fever** or ***extensive*** **cellulitis**; **Duration of therapy**; is **7 days**, *depending on* the **clinical response**.

MSSA SSTI		
Antibiotic	**Adult Dose**	**Child Dose**
Dicloxacillin	500 mg orally 4 times daily	25–50 mg/kg/d in 3–4 divided doses
Cephalexin	500 mg orally 4 times daily	25–50 mg/kg/d in 3–4 divided doses
Nafcillin or Oxacillin	1-2 g IV every 4 hours	100–150 mg/kg/d in 4 divided doses
Cefazolin	1 g IV every 8 hours	50 mg/kg/d in 3 divided doses
Clindamycin	300–450 mg orally 4 times daily OR 600 mg IV every 8 hours	25–30 mg/kg/d orally in 3 divided doses OR 25–40 mg/kg/d IV in 3 divided doses
Doxycycline	100 mg orally twice daily	Not recommended for age <8 years
Trimethoprim / Sulfamethoxazole	1–2 double strength tablets twice daily	8–12 mg/kg based on Trimethoprim in 4 divided doses IV or 2 divided doses orally
MRSA SSTI		
Vancomycin	30 mg/kg/d IV in 2 divided doses	40 mg/kg/d IV in 4 divided doses
Linezolid	600 mg orally or IV every 12 hours	<12 y; 10 mg/kg orally/IV every 12 hrs
Clindamycin	300–450 mg orally 4 times daily OR 600 mg IV every 8 hours	30–40 mg/kg/d orally in 3 divided doses OR 25–40 mg/kg/d IV in 3 divided doses
Daptomycin	4 mg/kg IV every 24 hours	Not Applicable (N/A)
Ceftaroline	600 mg IV every 12 hours	Not Applicable (N/A)
Doxycycline	100 mg orally twice daily	Not recommended for age <8 years
Trimethoprim / Sulfamethoxazole	1–2 double strength tablets twice daily	8–12 mg/kg based on Trimethoprim in 4 divided doses IV or 2 divided doses orally

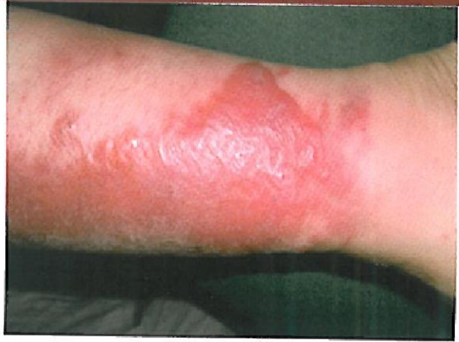
Empirical Therapy	
Moderate Cases	**Severe Cases**
Doxycycline OR Trimethoprim/Sulfamethoxazole	**Vancomycin OR Daptomycin OR Linezolid OR Telavancin OR Ceftaroline**

III) Cellulitis and Erysipelas



Cellulitis

- ***Acute spreading*** **skin infection** that involves primarily the ***deep* dermis** and **subcutaneous fat**.
- ***Non-elevated***, *poorly* **defined margins**.
- **Warmth**, **erythema** and **pain**.
- **Malaise**, **fever** and **chills**.
- *Usually*, **patient** has had ***previous*** **minor trauma**, **abrasions**, **ulcers**, or **surgery**.
- **Pathogen**; ***S. pyogenes*** and *occasionally* ***S. aureus***



Erysipelas

- ***Acute spreading*** **skin infection** that involves primarily the **superficial dermis**.
- **Edge** of **infection** is ***elevated*** and *sharp* **margins**.
- **Warmth**, **erythema** and **pain**.
- **Malaise**, **fever** and **chills**.
- *Usually* occurs in **infants** and ***older*** **adults**.
- Usually occurs on the **legs** & **feet** (**facial** is *less common*).
- **Pathogen**; ***S. pyogenes***

- **Pharmacotherapy** (***Recommendations***);

Cellulitis; Empirical Therapy for MSSA

- **Duration of therapy**; is **5-10 days**, may **extend therapy** if ***infection*** has ***not improved***.
  - * **Antistaphylococcal Penicillins**; **Nafcillin**, **Oxacillin** or **Dicloxacillin**.
  - * **Penicillin G** if *definitively* **streptococcal** (***drug of choice*** for ***S. pyogenes***)
  - * ***Alternatives***; **Clindamycin**, **β-lactamase Inhibitor Combinations** OR **1st generation Cephalosporin**.

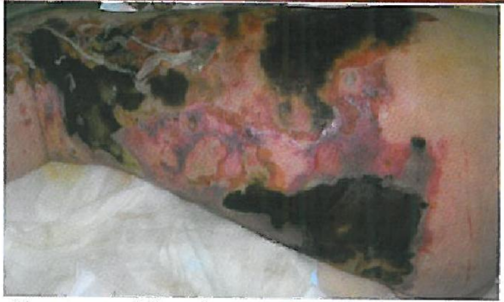
Cellulitis; Empirical Therapy for MRSA

- **Duration of therapy**; is **5-10 days**, may **extend therapy** if ***infection*** has ***not improved***.
  - * **Outpatient**: **Clindamycin**, **Trimethoprim/Sulfamethoxazole** (***add*** **β-lactam** for **Streptococcus**) OR **Doxycycline** (***add*** **β-lactam** for **Streptococcus**),
  - * **Inpatient**: **Vancomycin**, **Linezolid**, **Daptomycin** OR **Telavancin**.

Erysipelas; Empirical Therapy

- **Duration of therapy**; is **5 days**, may **extend therapy** if ***infection*** has ***not improved***.
  - * **Penicillin G**; ***Drug of choice***.
  - * **Clindamycin**; For **penicillin-allergic patients**.
  - * ***Alternatives***; **Penicillin V**, **Cephalexin**, **Nafcillin** OR **Cefazolin**.

IV) Necrotizing Fasciitis (NF)



- **Necrotizing fasciitis** (**NF**), *commonly known as* **flesh-eating disease**, is an ***infection*** that results in **death** of **body's soft tissue**.
- **Symptoms** *include* **acute**, ***necrotizing*** **cellulites**, **red** or **purple skin** in the affected area, ***severe*** **pain**, **fever** and **vomiting**.
- **Pathogen**; ***S. pyogenes*** is the ***major*** **cause**, but ***cases*** involve ***more than*** **one type** of **bacteria**.
- ***Delays*** in **surgery** are *associated with* a ***higher risk*** of **death** (**septic shock**).
- ***Because*** of the ***very high*** **mortality** *associated with* **necrotizing infections**, ***rapid*** and ***complete*** **debridement** (cutting away affected tissue) of ***all*** **devitalized** and **necrotic tissue** is ***essential***.
- ***Broad-spectrum*** **antibiotics** ***must*** **coverage** ***against*** **streptococci**, ***Enterobacteriaceae***, and **anaerobes**.
- **Computed Tomography** (**CT**) & **Magnetic Resonance Imaging** (**MRI**) are the ***best*** and ***most rapid*** **diagnosis**.
- **Pharmacotherapy** (***Recommendations***);
  - * **Surgical Debridement**; ***Most important*** **therapy** and often ***repeated*** **debridement** is **necessary**.
  - * **Antibiotic Empiric Therapy**: **Vancomycin** OR **Linezolid** PLUS **Piperacillin/Tazobactam** OR **Carbapenem** OR **Ceftriaxone** *with* **Metronidazole**.
  - * ***Streptococcal*** **necrotizing fasciitis**: ***High-dose*** IV **Penicillin** PLUS **Clindamycin**.

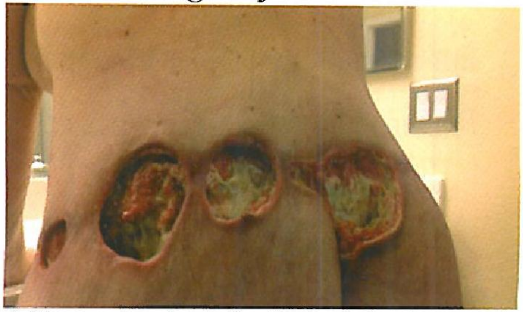
V) Diabetic Foot Infections

- **Foot infections** are the ***most common* problems** in *persons with* **diabetes.**
- *About* **25%** of **people** *with* **diabetes** *develop* **foot infections, 1** in **15** *requires* **amputation.**
- ***Pathophysiology***;
  - * **Neuropathy**; Motor and autonomic; lack of sensation
    - Mechanical or thermal injuries lead to ulcerations without patient knowledge.
    - Gait disturbances and foot deformities; maldistribution of weight on the foot.
    - Diminished sweating, causing dry, cracked skin.
  - * **Vasculopathy**; Decreased lower limb perfusion.
  - * **Immunologic defects**; Cellular and humoral.
- ***Pathogens***;

  - A) **Aerobes** 63–75%
    - * **Gram-positive** 42–64%
      - *Staphylococcus aureus* 15–20%
      - *Streptococcus* spp. 6–12%
      - *Enterococcus* spp. 7–20%
      - Coagulase-negative *staphylococci* 6–10%
      - Other gram-positive aerobes 0–12%
    - * **Gram-negative** 16–18%
      - *Proteus* spp. 5–6%
      - *Enterobacter* spp. 1–2%
      - *Escherichia coli* 3–5%
      - *Klebsiella* spp. 1–2%
      - *Pseudomonas aeruginosa* 1–3%
      - Other gram-negative bacilli 3–8%
  - B) **Anaerobes** 25–40%
    - * *Peptostreptococcus* spp. 8–12%
    - * Other *Bacteroides* spp. 3–6%
    - * Other anaerobes 7–10%
    - * *Bacteroides fragilis* group 4–7%
    - * *Clostridium* spp. 0–2%
- **Pharmacotherapy** (***Recommendations***);
  - A) **Preventive Therapy**; * ***Examine* feet *daily for* calluses, blisters, trauma** and so **forth.**
    - * ***Wear*** *properly* **fitting shoes.**
    - * ***Keep* feet *clean*** and ***dry.***
    - * ***No* barefoot walking.**
    - * ***Have* toenails *cut* properly.**
  - B) **Antimicrobial Therapy**;
    - **Treatment Duration**:
      - **1–2 weeks** for ***mild*** to ***moderate*** **infections.**
      - **2–3 weeks** for ***severe*** **infections.**
      - **4 weeks** or ***more*** is ***necessary*** for **osteomyelitis**;
      - ***After* amputation treatment, *duration*** is **2–5 days**; if there is ***no remaining* infected tissue** or **4 weeks** or ***more*** if **infected tissue *remains*.**
    - **Risk factors** *for* **MRSA** *include*; **history of MRSA infection** or **colonization,** ***high* local prevalence** of **MRSA**, or a ***severe*** **infection.**
    - **Risk factors** *for* ***Pseudomonas*** *include*; **patients *soaking* their feet,** ***lack*** **of response** to ***non*-pseudomonal therapy**, or a ***severe*** **infection.**
    - * **Mild infections** (and ***no* antibiotics** in the ***past* month**);
      - * **No MRSA *risk factors*: Penicillinase-resistant penicillin, First-generation Cephalosporin, Fluoroquinolone** OR **Clindamycin.**
      - * **MRSA *risk factors*: Doxycycline** OR **Trimethoprim/Sulfamethoxazole.**
    - * **Moderate** to **severe infections**;
      - * **Ampicillin/Sulbactam** OR **Ertapenem** OR **Cefoxitin** OR **Third-generation cephalosporin** OR **Moxifloxacin *alone*** OR **Ciprofloxacin/Levofloxacin** PLUS **Clindamycin** OR **Tigecycline.**
      - * If **risk** of ***P. aeruginosa***; **Piperacillin/Tazobactam** OR **Ceftazidime** OR **Cefepime** OR **Carbapenem.**
      - * If **risk** of **MRSA**; **Vancomycin** OR **Linezolid** OR **Daptomycin.**
  - C) **Surgical Therapy**; * **Drainage** and **debridement** (appropriate wound care) are ***very important.***
    - * **Amputation** is often ***necessary.***

VI) Pressure Injuries (Bedsores or Pressure Sore or Decubitus Ulcer)

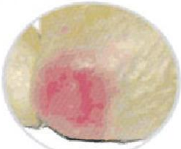
- The terms; **Bedsore**, **Pressure Sore** and **Decubitus Ulcer** are **used *interchangeably***.
- The terms **Decubitus Ulcer** (from *Latin* **decumbere**, **"to lie down"**).
- In April 2016, the National Pressure Ulcer Advisory Panel (NPUAP) announced that it was changing its preferred terminology from pressure ulcer *to* **Pressure Injury**, on the grounds that the latter term better described this injury process in both intact and ulcerated skin.
- ***Complications*** of **pressure injuries** are ***not* uncommon** and *may be* **life threatening**.



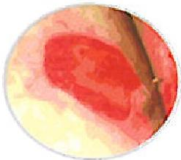
- ***Predisposing Factors***; **Paralysis**, **paresis**, **immobilization**, **malnutrition**, **anemia**, **infection**, and **advanced age**.
- **Pathophysiology**; Pressure injuries result from constant pressure sufficient to impair local blood flow to soft tissue for an extended period. This external pressure must be greater than the arterial capillary pressure (32 mm Hg) to impair inflow and greater than the venous capillary closing pressure (8-12 mm Hg) to impede the return of flow for an extended time.
- **Bacterial infections**, though ***not truly*** an **etiologic factor**, must be ***considered*** in the **treatment** of **pressure injuries**, **pathogens** *similar to* **diabetic foot infections**, a ***large variety*** of **microorganisms**.

STAGES

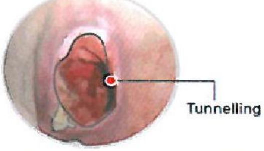
1 A bit of redness that doesn't lighten when pressed. Site might be painful, especially when touched.



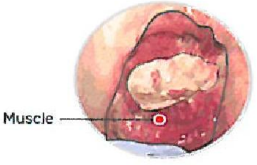
2 Part of the skin might have peeled off. The area looks like a blister, or a blister that has burst.



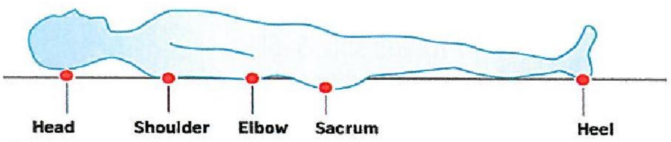
3 By now, it is a deep wound, often with some fat exposed. It looks like a crater, possibly with yellowish dead tissue at the bottom. If there is tunnelling, the wound would be deeper that what can be seen.



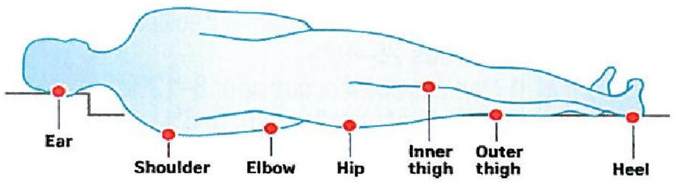
4 The wound is so deep that muscle, bone and tendon are exposed, with a significant amount of dead tissue at the base, either yellowish, or even dark and crusty.



WHERE THEY DEVELOP



Results from pressure, shearing force and friction.



Common sites are bony, prominent parts of the body.

PREVENTION AND TREATMENT

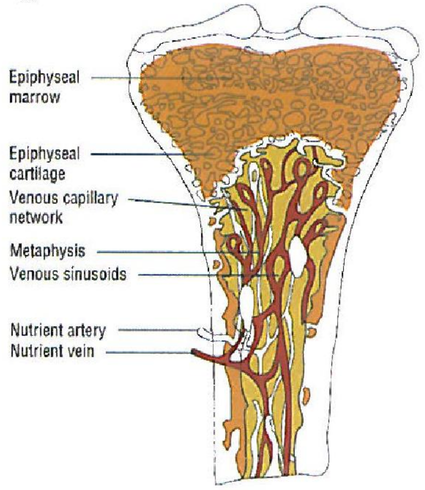
- Turn patient every two hours.
- Get patient out of bed – to walk or sit.
- Ensure sufficient nutrition and water intake.
- Change diapers at least every four hours.
- Apply moisturiser and cream that protects against moisture.
- Use cushions to reduce pressure.

- **Pharmacotherapy** (***Recommendations***);
  - **A) Pressure Reduction**;
    - * The first step in healing is determination of the cause (repositioning should be performed every 2 hours).
    - * Pressure reduction may be achieved through the use of specialized support surfaces for bedding and wheelchairs that can keep tissue pressures below 32 mm Hg.
  - **B) Pain Management**;
    - * Pain assessment should be completed, especially during repositioning, dressing changes & debridement.
  - **C) Wound Management**;
    - * Debridement; methods include sharp, mechanical, enzymatic and autolytic.
    - * Choice of wound dressings varies with the state of the wound.
    - * Wounds should be cleansed initially and with each dressing change; use of normal saline is preferred (Wound cleansing with antiseptic agents should be avoided because they destroy granulation tissue).
  - **D) Antimicrobials** and **Antibiotics**;
    - * Topical antibiotics, such as silver sulfadiazine cream, should be used for up to two weeks for clean ulcers that are not healing properly after two to four weeks of optimal wound care.
    - * Systemic antibiotics are not recommended unless there is evidence of advancing cellulitis, osteomyelitis, and bacteremia.
  - **E) Others**;
    - * Growth factors (e.g., platelet-derived growth factor becaplermin [Regranex®]) and vacuum-assisted closure for recalcitrant stage III and IV ulcers are emerging management options.
    - * The role of electromagnetic therapy, ultrasound, and hyperbaric oxygen therapy is unclear.

D) Bone and Joint Infections

I) Osteomyelitis (OM)

- **Osteomyelitis** is ***inflammation*** of the **bone** *caused by* an **infecting *organism***.
- *Although* **bone** is ***normally* resistant** to **bacterial colonization**, ***events*** such as **trauma**, **surgery**, the *presence of* **foreign bodies**, or the ***placement*** of **prostheses**; ***may*** **disrupt bony integrity** and ***lead to*** the ***onset*** of **bone infection**.
- ***All*** **bones** are *subject to* **infection**, the ***lower*** **extremity** is ***most commonly*** **involved**.
- **Osteomyelitis** ***generally*** is an **uncommon disease**.
- ***Pathogens***; ***Staphylococcus aureus*** is the ***most common*** (**MRSA** is ***common***), **Group A *streptococcus***, ***Streptococcus pneumoniae***, and ***Kingella kingae*** are the ***next* most common**.
- ***Signs*** and ***symptoms***;
  - * **Fever** and **chills**.
  - * ***Localized* pain**, **tenderness**, and **swelling**.
  - * **Neurologic symptoms** *if* **spinal cord *compression***.



Cross section of normal bone

- ***Classification*** of **Osteomyelitis**;

	Hematogenous Spread	Contiguous Spread	Vascular Insufficiency
Definition	- Spread of bacteria through the bloodstream from a distant site.	- Spread of bacteria from an adjacent tissue infection or by direct inoculation.	- Infection results from insufficient blood supply to fight the bacteria.
Patient population	- Adult: vertebrae - Children (<16 years): femur, tibia, humerus	- Adults (25–50 years): femur, tibia, skull	- Adults (>50 years)
Predisposing factors	- Bacteremia - Sickle cell anemia	- Open reduction of fractures - Gunshot wound - Dental or sinus infections - Soft tissue infections	- Diabetes - Peripheral vascular disease (PVD) - Post-Coronary Artery Bypass Graft (CABG)
Common pathogens	- Usually **monomicrobial** - Children: *Staphylococcus aureus* (60%–90%). - Adults: *S. aureus* and gram-negative bacilli - Sickle cell anemia: Salmonella (67%), *S. aureus*, *S. pneumoniae* - IV drug users: *P. aeruginosa*	- Usually **mixed infection**: - *S. aureus* (60%), - *S. epidermidis*, - *Streptococcus* - Gram-negative bacilli: *P. aeruginosa* (foot punctures), *Proteus, Klebsiella, E. coli* - Anaerobic (human bites, decubitus ulcers)	- Usually **polymicrobial**: - *S. aureus, S. epidermidis, Streptococcus* - Gram-negative bacilli - Anaerobic (*Bacteroides fragilis* group) - Infected prosthesis: *S. aureus, S. epidermidis.*

- ***Diagnosis***;
  - * **Laboratory tests**;
    - ***Elevated* WBC**.
    - ***Elevated* erythrocyte sedimentation rate (ESR)**.
    - ***Elevated* C-reactive protein (CRP)**.
  - * **Diagnostic tests**;
    - **Radiographic tests**: Positive results lag behind infectious process.
    - **Computed tomography (CT)** and **magnetic resonance imaging (MRI)** scans.
    - **Radionuclide imaging**: Positive as soon as 24–48 hours after infectious process begins.

Osteomyelitis of the 1st toe

- ***Pharmacotherapy*** (***Recommendations***);
  - * **Antibiotics *generally*** are **given** in ***high doses*** so that ***adequate* antimicrobial concentrations** are **reached *within* infected bone**.
  - * The ***standard*** **duration** of **antimicrobial treatment** for;
    - ***Acute* Osteomyelitis**; **4–6 weeks**.
    - ***Chronic* Osteomyelitis**; **6–8 weeks** of ***parenteral* therapy** and **3–12 months** of **oral therapy**.

* **Criteria** *for* **Effective Oral Therapy** *for* **Osteomyelitis**;

- Adherence.
- *Identified* **organism** that is ***highly*** **susceptible** to the **oral antibiotic used.**
- **C-reactive protein** ***less than*** **2.0 mg/dL.**
- *Adequate* **surgical debridement.**
- *Resolving* **clinical course.**

* **Empiric Therapy**;

A) **Neonates** < **1 month**;

   * **Nafcillin** PLUS **Cefotaxime** OR * **Nafcillin** PLUS an **Aminoglycoside.**

B) **Infants** **(1–36 months)**;

   * **Cefuroxime** OR * **Ceftriaxone** OR * **Nafcillin** PLUS **Cefotaxime.**

C) **Pediatrics** (> **3 years**);

   * **Nafcillin** OR * **Cefazolin** OR * **Clindamycin**

D) **Adults**;

   * **Nafcillin** OR * **Cefazolin** OR * **Vancomycin**

   * *Choose additional* **antibiotics** *according to* **patient-specific characteristics.**

E) **Patients** *with* **sickle cell anemia**; * **Ceftriaxone** OR * **Cefotaxime** OR * **Ciprofloxacin** OR * **Levofloxacin**

* **Prosthetic Joint Infections**;

A) ***Debridement*** and ***retention*** of **prosthesis** or **one-stage *exchange*** of **prosthesis**;

   * Staphylococcal: Pathogen-specific intravenous therapy plus rifampin 350–400 mg twice daily for 2–6 weeks, followed by rifampin plus ciprofloxacin or levofloxacin for 3 months (hip, elbow, shoulder, ankle prosthesis) or 6 months (knee prosthesis)

   * Non-staphylococcal: Pathogen-specific intravenous (or highly bioavailable oral) therapy for 4–6 weeks, followed by indefinite oral suppression therapy.

B) ***Resection*** of **prosthesis** *with* or *without* **planned *re-implantation*** or ***amputation***;

   * Pathogen-specific intravenous (or highly bioavailable oral) therapy for 4–6 weeks.

   * Only 24–48 hours of antibiotic therapy after amputation if all infected tissue is removed.

II) Infectious Arthritis or Septic Arthritis

- **Septic Arthritis** or **Infectious Arthritis** is a ***direct*** **invasion** of **joint space** by *various* **microorganisms**, *most commonly* caused by **bacteria.**
- **Smears** of the **synovial fluid** can be useful to ***select*** appropriate **antibiotic therapy *initially*.**
- **Antibiotics *should be*** **initiated early** *because* of the ***high risk*** for ***long-term*** **complications.**
- The ***most important*** **therapeutic measures** of ***infectious*** **arthritis** are;
  1) *Appropriate* **antibiotics.**
  2) **Joint drainage.**
  3) **Joint rest.**
- **Pharmacotherapy** (***Recommendations***);

* **Empiric Therapy**; ***All regimens*** are *given* **IV.**

- Empiric therapy *should be* guided *by* results of synovial fluid Gram staining.
- *Initial* therapy *should consist* of IV antibiotics.
- The ***duration*** of **empiric therapy** *depends on* the ***determination of*** the ***specific*** **etiology.**

A) **Gram-positive cocci** in ***clusters***; **Vancomycin.**

B) **Gram-positive cocci** in ***chains***; **Ampicillin** OR **Ceftriaxone** OR **Vancomycin** (if patient is allergic to penicillin).

C) **Gram-negative cocci**; **Ceftriaxone** OR **Ciprofloxacin** (only if susceptibility testing will be available).

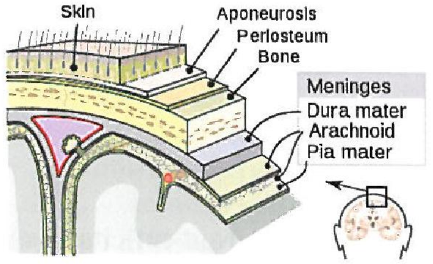
D) **Gram-negative rods**; **Ceftriaxone** OR **Cefepime** OR **Piperacillin/Tazobactam** OR **Aztreonam** OR **Ciprofloxacin** OR **Levofloxacin**

E) **Gram stain negative** or ***unavailable***; **Vancomycin** PLUS **Ceftriaxone** OR **Vancomycin** PLUS **Cefepime** (if *Pseudomonas* is suspected).

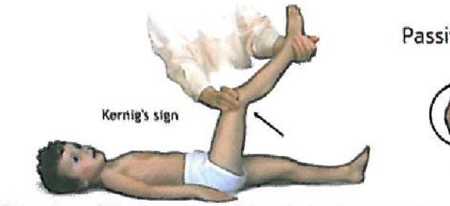
E) Central Nervous System Infections

Meningitis

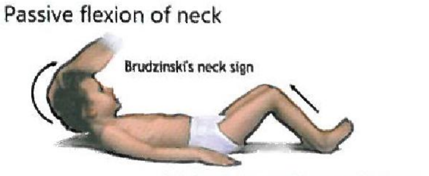
- **Central Nervous System** (**CNS**) **infections** are caused by a ***variety*** of **pathogens**, *including* **bacteria**, **viruses**, **fungi** and **parasites**.
- ***Newer*** **diagnostic techniques** have *enabled **more rapid*** and ***definitive*** **diagnoses**, thus ***diminishing*** the ***number*** of **unknown diagnoses** and ***improving*** **targeted therapy**.
- **Meningitis** is an ***acute*** **inflammation** of the ***protective*** **membranes** ***covering*** the **brain** and **spinal cord**, known collectively as the **meninges**.
- The ***inflammation*** may be *caused by* **infection** *with* **viruses**, **bacteria**, **fungi** and **parasites** and ***less commonly*** by ***certain*** **drugs**.
- *Approximately* **1.2 million** *cases* of ***acute*** **bacterial meningitis**, *excluding* epidemics, occur ***every*** **year** around the **globe**, resulting in **135,000 deaths**.



- ***Causes***; **A) Bacterial** (**Septic Meningitis**); *See recommendations.*
  B) Other causes (**Aseptic Meningitis**);
    - **Viral**;. Herpes simplex virus, enteroviruses, varicella zoster virus, mumps virus, HIV, and Lymphocytic choriomeningitis (LCM).
    - **Fungal**; Most common; *Cryptococcus neoformans* and *Candida* spp.
    - **Parasitic**; Most common; *Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, *Schistosoma*.
    - **Tubercular**; *Mycobacterium tuberculosis*.
    - **Syphilis**; *Treponema pallidum*.
    - **Drugs**; **Drug-induced meningitis (DIAM)** is ***unknown***.
        - Many antimicrobials can cause (e.g., Trimethoprim/Sulfamethoxazole, Ciprofloxacin, Cephalexin, Metronidazole, Amoxicillin, Penicillin and Isoniazid).
        - Other drugs; NSAIDs, Ranitidine, Carbamazepine, Vaccines against hepatitis B and mumps and IV immunoglobulins.
- ***Predisposing Factors***;
    - Head trauma
    - Cerebrospinal fluid (CSF) fistula or leak
    - Splenectomized patients
    - Immunosuppression
    - Neurosurgical patients
    - Sickle cell disease
    - CNS shunts
    - Alcoholism
    - Congenital defects
    - Local infections; Sinusitis, otitis media, pharyngitis and bacterial pneumonia
- ***Signs***;
    - **Brudzinski** *sign*
    - **Kernig** *sign*
    - **Bulging fontanel**

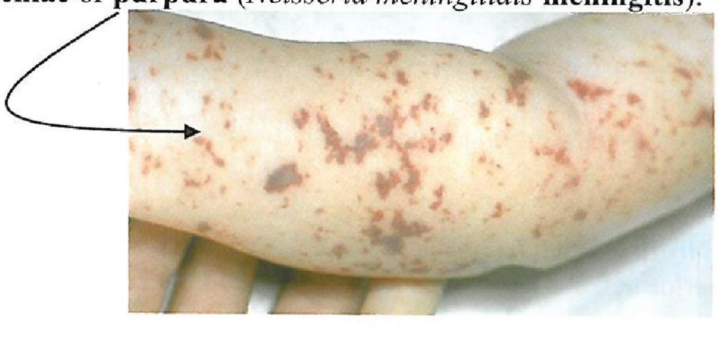


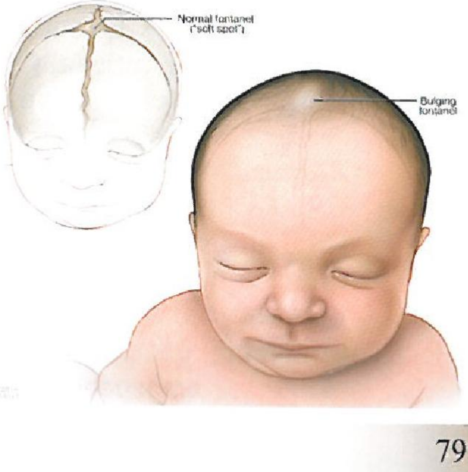
Extension of the knee is painful or limited in extension



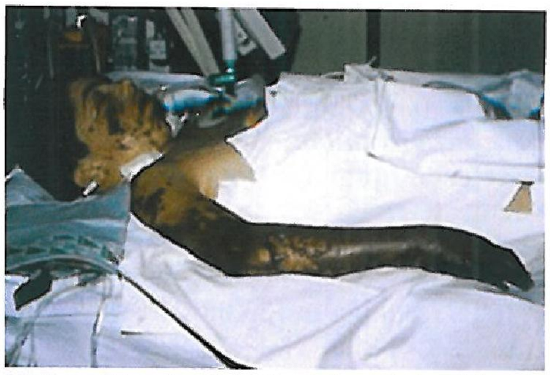
Elicits hip and knee flexion

- ***Symptoms***;
    - **Fever** and **chills**.
    - **Headache**, **backache**, **nuchal rigidity** (neck stiffness), **mental status changes**, **photophobia**.
    - **Nausea**, **vomiting**, **anorexia**, **poor feeding habits** (infants).
    - **Petechiae** or **purpura** (*Neisseria meningitidis* **meningitis**).





- ***Complications***;
  - **A**) ***Early* complications**;
    - * **Septic shock**; including **disseminated intravascular coagulation** (**DIC**).
    - * **Coma** *with loss* of **protective airway *reflexes***.
    - * **Seizures**; which occur in 30-40% of children and 20-30% of adults.
    - * **Cerebral edema**.
    - * **Septic arthritis**.
    - * **Pericardial effusion**.
    - * **Hemolytic anemia** (*Haemophilus influenzae*).
  - **B**) ***Delayed* complications**;
    - * ***Decreased* hearing** or **deafness**.
    - * **Cranial nerve *dysfunctions***.
    - * ***Multiple* seizures**.
    - * **Focal paralysis**.
    - * **Subdural effusions**.
    - * **Hydrocephalus**.
    - * **Intellectual deficits** (learning disability & mental retardation)
    - * **Ataxia**.
    - * **Blindness**.
    - * **Waterhouse-Friderichsen syndrome**; adrenal gland failure (bleeding into the adrenal glands).
    - * ***Peripheral* gangrene**.



- ***Diagnosis***;
  - **A**) **History** and **physical examination**.
  - **B**) **Lumbar puncture**;
    - * ***Elevated* opening pressure** (>25 cm H_2O).
    - * **CSF *Changes***;

Component	Normal CSF	Bacterial	Viral	Fungal	Tuberculosis
WBC	0–5 cells/μL (Lymphocytes)	>1000 cells/μL (>80% PMNs)	10-300 cells/μL (Lymphocytes)	10-200 cells/μL (Lymphocytes)	100–500 cells/μL (Lymphocytes)
Glucose	30–70 mg/dL (>60% of serum)	Low (< 40% of serum)	Usually normal	Low	Low
Protein	< 45 mg/dL	>150 mg/dL	< 100 mg/dL	50–150 mg/dL	50–150 mg/dL

- PMNs; Polymorphonuclear neutrophils.

* **3 findings** on **CSF analysis** have clinically ***useful*** likelihood ratios for the **diagnosis** of **bacterial meningitis** in **adults**;
  1) CSF glucose-to-blood glucose ratio of 0.4 or lower.
  2) CSF WBC count of 500/μL or higher.
  3) CSF lactate level of 31.53 mg/dL or higher.

- **C**) **CSF stains** and **studies**;
  - * **Gram stain**; *Helps* **identify organism** in **60–90%** of **cases**.
  - * **Latex agglutination**: *High* **sensitivity**, **50–100%**, for ***common* organisms**.
    - * Not recommended routinely
    - * Most useful in patients pretreated with antibiotics with subsequent negative CSF Gram stains and cultures.
  - * **Acid-fast staining**; **Tubercular Meningitis**.
  - * **India ink test**; **Cryptococcal Meningitis**.
  - * **Cryptococcal antigen**; **Cryptococcal Meningitis**.
  - * **Herpes simplex virus polymerase chain reaction** (**PCR**); **HSV Meningitis**.
- **D**) **Laboratory Findings**;
  - * ***Elevated* WBC** with a ***left* shift** (increase in the number of immature WBCs; small WBCs).
  - * **CSF Gram stain**
  - * **CSF cultures** (positive in 75–80% of bacterial meningitis cases).
  - * **Blood cultures** (±)
  - * **C-reactive protein** (**CRP**).
- **E**) **Neuroimaging**; **Computed tomography** (**CT**) of the **head** and **magnetic resonance imaging** (**MRI**) of the **brain** *generally* **are performed** at a ***later stage*** to assess for **complications** of **meningitis**.

- **Pharmacotherapy** (***Recommendations***);

A) **Empiric Therapy**;

Predisposing Factor	Common Bacterial Pathogens	Antimicrobial Therapy
Age		
<1 month	*Streptococcus agalactiae* *Escherichia coli* *Listeria monocytogenes* *Klebsiella species*	**Ampicillin** PLUS **Cefotaxime** OR **Ampicillin** PLUS an **Aminoglycoside**
1–23 months	*Streptococcus pneumoniae* *Neisseria meningitidis* *Streptococcus agalactiae* *Haemophilus influenzae* *Escherichia coli*	**Vancomycin** PLUS **Third-generation Cephalosporin** (**Cefotaxime** OR **Ceftriaxone**)
2–50 years	*Neisseria meningitidis* *Streptococcus pneumoniae*	
>50 years	*Streptococcus pneumoniae* *Neisseria meningitidis* *Listeria monocytogenes* Aerobic gram-negative bacilli	**Vancomycin** PLUS **Ampicillin** PLUS **Third-generation Cephalosporin** (**Cefotaxime** OR **Ceftriaxone**)
Head trauma		
Basilar skull fracture	*Streptococcus pneumoniae* *Haemophilus influenzae* *Streptococcus pyogenes*	**Vancomycin** PLUS **Third-generation Cephalosporin**
Penetrating trauma	*Staphylococcus aureus* *Staphylococcus epidermidis* Aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	**Vancomycin** PLUS **Cefepime** OR **Ceftazidime** OR **Meropenem**
Post-Neurosurgery		
CSF shunt		

B) **Therapy for Common Pathogens**;

Microorganism, susceptibility	Standard Therapy	Alternative Therapies
Streptococcus pneumoniae	Duration of Therapy: Based on clinical experience; 10-14 days	
Penicillin MIC = < 0.1 µg/mL	**Penicillin G**; 4 million IU IV/4 hrs OR **Ampicillin**; 2 g IV every 4 hrs	**Third-generation Cephalosporin** OR **Chloramphenicol**
Penicillin MIC = 0.1–1.0 µg/mL	**Third-generation Cephalosporin**	**Cefepime** OR **Meropenem**
Penicillin MIC = ≥2.0 µg/mL	**Vancomycin** PLUS **Third-generation Cephalosporin**	**Fluoroquinolone**; **Moxifloxacin**
Neisseria meningitidis (7 days)		
Penicillin MIC = < 0.1 µg/mL	**Penicillin G** OR **Ampicillin**	**Third-generation Cephalosporin** OR **Chloramphenicol**
Penicillin MIC = 0.1–1.0 µg/mL	**Third-generation Cephalosporin**	**Chloramphenicol** OR **Fluoroquinolone** OR **Meropenem**
Haemophilus influenzae (7 days)		
β-Lactamase negative	**Ampicillin**	**Third-generation Cephalosporin** OR **Cefepime** OR **Chloramphenicol** OR **Fluoroquinolone**
β-Lactamase positive	**Third-generation Cephalosporin**	**Cefepime** OR **Chloramphenicol** OR **Fluoroquinolone**
Listeria monocytogenes (≥21 d)	**Ampicillin** OR **Penicillin G**	**Trimethoprim/Sulfamethoxazole** OR **Meropenem**
Streptococcus agalactiae (14-21)	**Ampicillin** OR **Penicillin G**	**Third-generation Cephalosporin**
Escherichia coli and other *Enterobacteriaceae*	**Third-generation Cephalosporin**	**Aztreonam** OR **Fluoroquinolone**, OR **Meropenem**, OR **Ampicillin** **Trimethoprim/Sulfamethoxazole**
Pseudomonas aeruginosa	**Cefepime** OR **Ceftazidime**	**Aztreonam** OR **Ciprofloxacin** OR **Meropenem**

C) Adjunctive Corticosteroid Therapy; **Dexamethasone use** in **children** with ***Haemophilus influenzae* meningitis** or in **adults** with ***Streptococcus pneumoniae* meningitis**; however, may need to initiate before knowing specific causative bacteria.

- *** Benefits**;
  - **Significantly *less* hearing loss** and other **neurologic sequelae** in **children** *receiving* **Dexamethasone** for ***Haemophilus influenzae* meningitis**.
  - **Significantly *improved* outcomes**, *including* ***decreased* mortality**, in **adults** *receiving* **Dexamethasone** for ***Streptococcus pneumoniae* meningitis**.
- *** Risks**; May decrease **antibiotic *penetration*** (decreased penetration of Vancomycin in animals after Dexamethasone).
- *** Dose**; **Dexamethasone 0.15 mg/kg *every* 6 hours** for **2–4 days** (10–20 minutes before or at same time as antibiotics).

- **Prophylaxis (*Recommendations*)**;

Streptococcus pneumoniae

- **Vaccines**;
  - **Pneumococcal Polysaccharide Vaccine (PPSV23)** (**Pneumovax®23**) or/and **Pneumococcal Conjugate Vaccine (PCV13)** (**Prevnar-13®**);
    - ***All children*** **<2 years old.**
    - ***All adults*** **≥ 65 years old.**
    - **People 2-64 years old *with certain* medical conditions.**

Neisseria meningitidis

A) Vaccines;

- *** Types**;
  - **Meningococcal Polysaccharide Vaccine** (**Menomune®**); lack serogroup B.
  - **Meningococcal Conjugate Vaccine** (**Menactra®** and **Menveo®**); lack serogroup B.
    - * ***Indications***;
      - All preteens and teens at 11 to 12 years old with a booster dose at 16 years old.
      - Children and adults at increased risk for meningococcal disease.
  - **Serogroup B Meningococcal Vaccines** (**Bexsero®** and **Trumenba®**).
    - * ***Indications***; People 10 years or older at increased risk for meningococcal disease.
- *** *Other* Indications**;
  - College freshmen living in dormitories (4 cases per 100,000 per year, especially freshmen living in dormitories).
  - Military recruits.
  - Travel to "meningitis belt" of Africa and Asia, Saudi Arabia for Islamic Hajj pilgrimage.
  - People with asplenia (anatomic or functional).
  - People with terminal complement component deficiencies.
  - Outbreaks of meningococcal disease.

B) Chemoprophylaxis; *For* **close contacts** (household or day care) and **exposure** to **oral secretions** of **index case**;

- *** Rifampin**;
  - **Adults**; **600 mg *every* 12 hours × 4 doses.**
  - **Children**; **10 mg/kg *every* 12 hours × 4 doses.**
  - **Infants** (< 1 month); **5 mg/kg *every* 12 hours × 4 doses.**
- *** Ciprofloxacin**; **500 mg orally** as **single *dose*** (adults only).
- *** Ceftriaxone**; **125–250 mg IM** as **single *dose*.**

Haemophilus influenzae

A) Vaccines; ***Haemophilus influenzae* Type B (Hib) Polysaccharide Vaccine**; * ***Indications***;

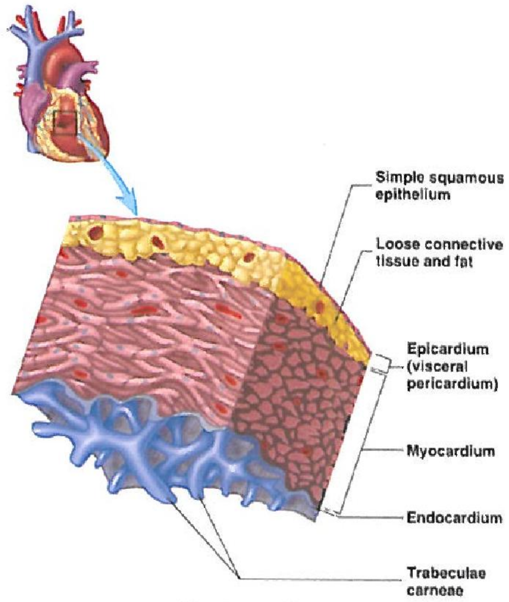
- All children younger than 5 years old.
- Some people at increased risk for invasive Hib disease.
- Unvaccinated older children and adults with certain medical conditions.

B) Chemoprophylaxis;

- **Adults**: **Rifampin 600 mg/day *for* 4 days.**
- **Children** (1 month to 12 years): **Rifampin 20 mg/kg/day *for* 4 days.**
- **Infants** (<1 month): **Rifampin 10 mg/kg/day *for* 4 days.**

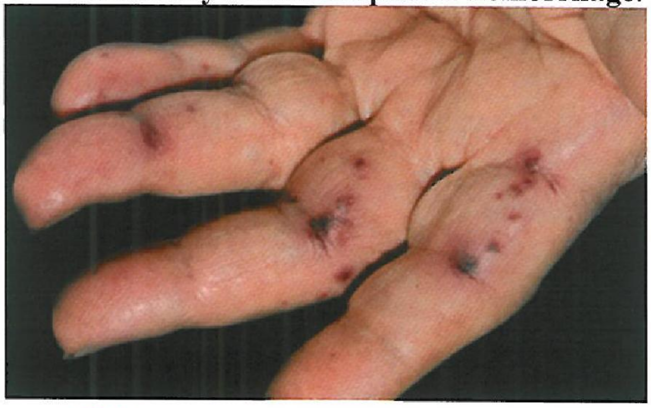
F) Infective Endocarditis (IE)

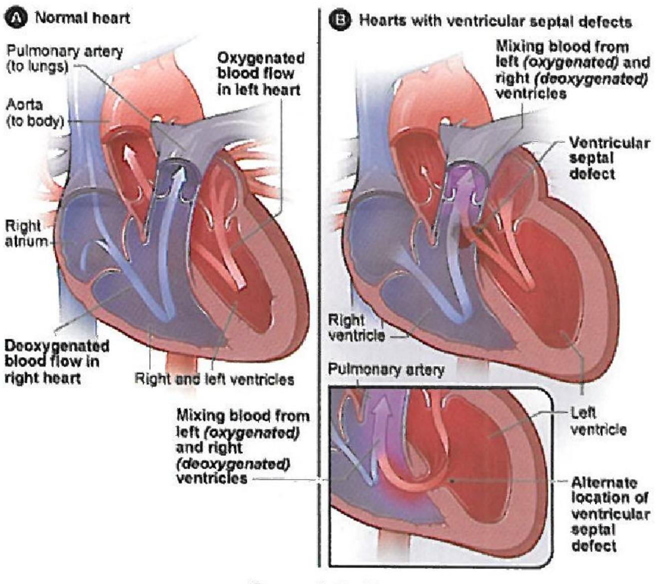
- **Endocarditis** is an ***inflammation*** of the **endocardium**, the **membrane *lining*** the **chambers** of the **heart** and ***covering*** the **cusps** of the **heart valves**.
- **Infective endocarditis** is an ***infection*** of the **endocardial surface** of the **heart (endocardium)**, which may *include **one*** or ***more*** **heart valves**, the **mural endocardium**, or a **septal defect**.
- **Intracardiac effects** *include **severe*** **valvular insufficiency**, which may *lead to **intractable*** **congestive heart failure** and **myocardial abscesses**. If **left *untreated*, infective endocarditis** is ***almost*** **inevitably fatal**.
- ***Prevalence***; *about* **5 cases** *per* **100,000 persons** *per* **year**. The ***risk of*** **death** among those **infected** is about **25%**.
- ***Pathophysiology***;
  - The development of infectious endocarditis requires the presence of bacteria or fungi in the blood and an intracardiac surface on which these microorganisms can attach.
  - Mechanical and biomechanical prosthetic heart valves can serve as foci for platelet adhesion and thrombus formation.
  - These sites in turn provide extra surface area to which microorganisms can adhere and form vegetations.


Simple squamous epithelium
Loose connective tissue and fat
Epicardium (visceral pericardium)
Myocardium
Endocardium
Trabeculae carneae

Endocardium

- ***Signs*** & ***symptoms***;
  - * **Fever**: Low grade & remittent; 90% of patients.
  - * **Cardiac murmur**; 90% of patients.
  - * **Cutaneous *manifestations*** (50% of patients); **petechiae** *(including* **conjunctival)**, **Janeway lesions** & **splinter hemorrhage**.




A Normal heart
Pulmonary artery (to lungs)
Aorta (to body)
Oxygenated blood flow in left heart
Right atrium
Deoxygenated blood flow in right heart
Right and left ventricles
Mixing blood from left (oxygenated) and right (deoxygenated) ventricles
B Hearts with ventricular septal defects
Mixing blood from left (oxygenated) and right (deoxygenated) ventricles
Ventricular septal defect
Right ventricle
Pulmonary artery
Left ventricle
Alternate location of ventricular septal defect

Septal Defect

  - * **Others**;
    - Arthralgias, myalgias, low back pain and arthritis.
    - Fatigue, anorexia, weight loss and night sweats.
- ***Risk factors***;
  - **Prosthetic heart valves** (highest risk).
  - ***Previous*** **endocarditis** (highest risk).
  - **Intracardiac devices** (such as Implantable cardioverter-defibrillators).
  - **Rheumatic heart disease**; *repeated* ***Streptococcus pyogenes*** **infection**.
  - **Age-related degenerative valvular lesions.**
  - **Congenital heart disease.**
  - **Hemodialysis** and **IV drug use**
  - **Immunocompromised & Diabetes patients**
- ***Laboratory Findings***;
  - * **Anemia**; *normochromic, normocytic.*
  - * **Leukocytosis** (Increase total WBCs count).
  - * ***Elevated*** **ESR** and **CRP**.
  - * ***Positive*** **blood culture** in 78–95% of patients.
- ***Cardiac imaging***; *commonly* **performed**.
- ***Most common Complications***;
  - * **Congestive heart failure**: 38–60% of patients.
  - * **Emboli**: 22–43% of patients.
  - * **Mycotic aneurysm**: 5–10% of patients.
- ***Most Common Pathogens***;
  - * *Streptococcus*; 50%
  - * Coagulase-negative *Staphylococcus*; 7%
  - * *Staphylococcus aureus*; 25%
  - * Gram-negative bacilli; 6%
  - * *Enterococcus*; 8%
  - * *Candida albicans*; 2%

- **Pharmacotherapy** (***Recommendations***);

Organism	**Recommended Therapy**	**Duration (weeks)**	
		Native Valve	Prosthetic Valve
Viridans Group Streptococci (VGS) and *Streptococcus gallolyticus (bovis)*;			
Penicillin MIC ≤ 0.12 mcg/mL (Native & Prosthetic Valve)	**Penicillin G** Adult; 12-18 million (Pediatric; 200,000 units/kg) [Adult; 24 million in Prosthetic Valve] IU/24 h IV in 1 dose or in 4–6 equally divided doses	4	6
	Ceftriaxone Adult; 2 g (Pediatric; 100 mg /kg)/24 h IV/IM/1 dose	4	6
	Penicillin G PLUS **Gentamicin** Gentamicin; 3 mg/kg per 24 h IV or IM in 1 dose	2	2
	Ceftriaxone PLUS **Gentamicin**	2	2
	Vancomycin 30 mg/kg/ per 24 h IV in 2 equally divided doses	4	6
Penicillin MIC > 0.12 mcg/mL (Only in Prosthetic Valves)	**Penicillin G** PLUS **Gentamicin**	-	6
	Ceftriaxone PLUS **Gentamicin**	-	6
	Vancomycin	-	6
Oxacillin-sensitive *Staphylococcus aureus*	**Oxacillin** OR **Nafcillin** (**Cefazolin**; **penicillin-allergic**) ± **Gentamicin** for 3–5 days (+ prosthetic valve) [PLUS **Rifampin** in prosthetic valves]	6	≥6
Oxacillin/Nafcillin; Adult; 12g (Pediatric; 200 mg/kg)/24 h IV in 4–6 equally divided doses **Cefazolin**; Adult; 6 g (Pediatric; 100 mg/kg)/24 h IV in 3 equally divided doses **Rifampin**; Adult;900 mg (Pediatric; 20 mg/kg)/24 hours IV/orally in three equally divided doses			
Oxacillin-resistant *Staphylococcus aureus*	**Vancomycin**; Only in Native Valves **Vancomycin** PLUS **Rifampin** PLUS **Gentamicin** (for 2 weeks) in prosthetic valves	6	≥6
	Daptomycin ≥8 mg/kg/dose; Only in Native Valves	6	-
Enterococcus (Streptomycin used in strains resist Gentamicin)	**Penicillin G** OR **Ampicillin** PLUS **Gentamicin** OR **Streptomycin**	4–6	6
	Vancomycin PLUS **Gentamicin** OR **Streptomycin**	6	6
Enterococcus; Penicillin resistant strains	**Ampicillin/Sulbactam** OR **Vancomycin** PLUS **Gentamicin**	6	6
Enterococcus faecium; Penicillin, Aminoglycoside and Vancomycin resistant	**Linezolid** OR **Daptomycin** OR **Quinupristin/Dalfopristin**	≥8	≥8
Enterococcus faecalis; Penicillin, Aminoglycoside and Vancomycin resistant	**Imipenem/Cilastatin** PLUS **Ampicillin**	≥8	≥8
	Ceftriaxone PLUS **Ampicillin**	≥8	≥8
HACEK group (*Haemophilus*, *Actinobacillus* *Cardiobacterium*, *Eikenella* and *Kingella*)	**Ceftriaxone**	4	6
	Ampicillin/Sulbactam	4	6
	Fluoroquinolone (**Ciprofloxacin**, **Levofloxacin**, **Moxifloxacin**)	4	6

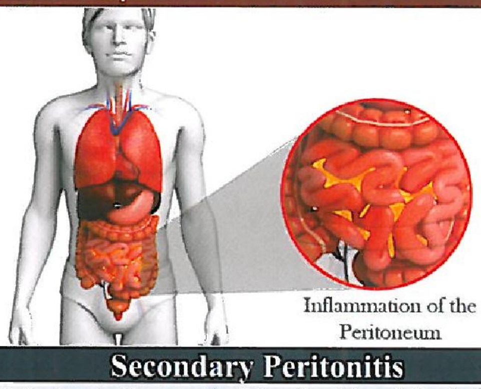
- **Antibiotics** for **Prophylaxis** for **Dental** or **Respiratory Tract Procedures**;
  - **Standard general prophylaxis**; **Amoxicillin** (Adults: 2 g; children: 50 mg/kg 1 hour before procedure).
  - **Unable to take oral medications**; **Ampicillin** (Adults: 2 g; child: 50 mg/kg IM/IV, 30 min before procedure)
  - **Allergic to penicillin**;
    - * **Clindamycin** (Adults: 600 mg; children: 20 mg/kg 1 hour before procedure).
    - * **Cephalexin** (Adults: 2 g; children: 50 mg/kg 1 hour before procedure).
    - * **Azithromycin** or **Clarithromycin** (Adults: 500 mg; children: 15 mg/kg 1 hour before procedure).
  - **Allergic to penicillin and unable to take oral medications**;
    - * **Clindamycin** (Adults: 600 mg; children: 20 mg/kg IV within 30 minutes before procedure)
    - * **Cefazolin** or **Ceftriaxone** (Adults: 1 g IM/IV; children: 50 mg/kg IM/IV within 30 minutes before procedure)

G) Intra-abdominal Infections

- **Intra-abdominal infections** are the ***second*** **most common** cause of cause of ***severe*** **sepsis** and ***mortality*** in **intensive care units (ICU).**
- ***Complicated*** **intra-abdominal infection**, which ***extends into*** the **peritoneal** ***space***, is *associated with* **abscess** ***formation*** and **peritonitis.**
- ***Uncomplicated*** **infection**, which ***involves*** **intramural inflammation** of the **gastrointestinal tract**, may *progress to* ***complicated*** **infection** if ***left*** **untreated.**

Peritonitis and Abdominal Sepsis

- **Peritonitis** is an ***inflammation*** of the **peritoneum (serosal membrane** that ***lines*** the **abdominal cavity).**
- **Peritoneal infections** are *classified as*;
  - A) **Primary**; ***Spontaneous*** or **idiopathic**, seen *mostly* in **patients** with **chronic liver** ***disease.***
  - B) **Secondary**; *Occurs* ***secondary*** to an **abdominal process.**
  - C) **Tertiary**; ***Persistent*** or ***recurrent*** **infection** ***after*** **adequate** ***initial*** **therapy.**



Inflammation of the Peritoneum

	Primary (Spontaneous) Peritonitis	Secondary Peritonitis
Etiology	- Alcoholic cirrhosis & ascites (10%). - Other; commonly to ascites. * Post-necrotic cirrhosis. * Chronic active hepatitis. * Acute viral hepatitis. * Congestive heart failure. * Systemic lupus erythematous. * Metastatic malignancy.	- Injuries to the gastrointestinal tract, including; * Peptic ulcer perforation * Perforation of a gastrointestinal organ * Appendicitis * Endometritis secondary to intrauterine device * Bile peritonitis * Pancreatitis * Operative contamination * Diverticulitis * Intestinal neoplasms * Secondary to peritoneal dialysis
Common Pathogens	*Escherichia coli* *Klebsiella pneumoniae* *Streptococcus pneumoniae* *Streptococcus pyogenes*	A) **Stomach** & **proximal small intestine**; aerobic, and may gram +ve and gram -ve. B) **Ileum**: *E. coli*, *Enterococcus*, anaerobes. C) **Large intestine**: anaerobes, aerobic and may gram +ve and gram -ve.
Clinical Manifestations	- Fever - Abdominal pain - Nausea, vomiting, diarrhea - Diffuse abdominal tenderness, rebound tenderness, hypoactive or no bowel sounds.	- Fever, tachycardia - Abdominal pain aggravated by motion, rebound tenderness - Pain with breathing - Bowel paralysis - Decreased renal perfusion
Laboratory Evaluation	**Ascitic Fluid** * **Protein**: Low * **WBC** > 500 cells/μL * pH: Less than 7.35 * Lactic dehydrogenase: > 25 mg/dL * Gram stain: 60–80% are negative, but diagnostic if it is positive	**Ascitic Fluid** * **Protein**: High; >3 g/dL * **WBC** > 500 cells/μL

- ***Initial Evaluation***;
  * Routine history, physical examination and laboratory studies will identify most patients with suspected intra-abdominal infection.
  * For selected patients diagnostic imaging and computed tomography (CT) scan may be performed.

- ***Fluid Resuscitation***;
  - * **Patients *should*** undergo ***rapid* restoration** of **intravascular volume** and ***additional* measures** as needed to ***promote* physiological stability**.
- ***Antimicrobial Therapy***;
  - * **Antimicrobial therapy *should be* initiated *once*** a **patient *receives*** a **diagnosis** of an **intra-abdominal infection** or ***once*** such an **infection** is **considered *likely***.
  - * **Initial Empiric Therapy**; **Therapy duration: 4–7 days** (*unless source control is difficult*)

Community-Acquired Complicated Intra-abdominal Infections			
Regimens	**Pediatric Patients**	**Mild to moderate**	**High-risk or Severe**
Single agent	* Ertapenem * Meropenem * Imipenem/Cilastatin * Ticarcillin/Clavulanate * Piperacillin/Tazobactam	* Cefoxitin * Ertapenem * Moxifloxacin * Tigecycline * Ticarcillin/Clavulanate	* Imipenem/Cilastatin * Meropenem * Doripenem * Piperacillin/Tazobactam
Combination	* Ceftriaxone OR Cefotaxime OR Cefepime OR Ceftazidime PLUS Metronidazole * Gentamicin OR Tobramycin PLUS Metronidazole OR Clindamycin ± Ampicillin	* Cefazolin OR Cefuroxime OR Ceftriaxone OR Cefotaxime OR Ciprofloxacin OR Levofloxacin PLUS Metronidazole	* Cefepime OR Ceftazidime OR Ciprofloxacin OR Levofloxacin PLUS Metronidazole

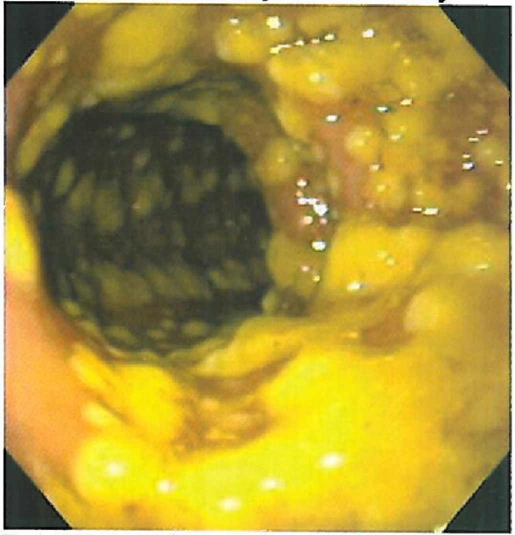
Health Care–Associated Complicated Intra-abdominal Infections				
	< 20% resistant *Pseudomonas aeruginosa*, ESBL-producing Enterobacteriaceae, *Acinetobacter*, or other MDR Gm -ve bacilli	ESBL-producing Enterobacteriaceae	*P.* aeruginosa > 20% resistant to Ceftazidime	MRSA
Carbapenem	Recommended	Recommended	Recommended	Not
Piperacillin/Tazobactam	Recommended	Recommended	Recommended	Not
Ceftazidime OR Cefepime PLUS Metronidazole	Recommended	Not	Not	Not
Aminoglycoside	Not	Recommended	Recommended	Not
Vancomycin	Not	Not	Not	Recomm.

MDR = Multidrug resistant
ESBL = Extended-spectrum beta-lactamase

Biliary Infection in Adults	
Community-acquired acute cholecystitis of mild-to-moderate severity	**Cefazolin OR Cefuroxime OR Ceftriaxone**
Community-acquired acute cholecystitis of severe physiologic disturbance, advanced age, or immunocompromised state	**Imipenem/Cilastatin OR Meropenem OR Doripenem Piperacillin/Tazobactam OR Ciprofloxacin OR Levofloxacin OR Cefepime PLUS Metronidazole**
Acute cholangitis after biliary-enteric anastomosis (any severity)	**Imipenem/Cilastatin OR Meropenem OR Doripenem OR Piperacillin/Tazobactam OR Ciprofloxacin OR Levofloxacin OR Cefepime PLUS Metronidazole**
Health care–associated biliary infection of any severity	**Imipenem/Cilastatin OR Meropenem OR Doripenem OR Piperacillin/Tazobactam, Ciprofloxacin OR Levofloxacin OR Cefepime PLUS Metronidazole PLUS Vancomycin**

H) *Clostridium difficile* Infection (CDI)

- ***Clostridium difficile* infection** (**CDI**) *results from* a ***disturbance*** of the ***normal*** **bacterial flora** of the **colon**, ***colonization*** by ***Clostridium difficile***, and the ***release*** of **toxins** that cause ***mucosal*** **inflammation**.
- **Antibiotic therapy** is the ***key factor*** that alters the **colonic flora**.
- **CDI** occurs ***primarily*** in **hospitalized patients**.
- In **United States CDI** is ***responsible for*** *approximately* **3 million cases** of **diarrhea** and **colitis** *annually* and **14,000 American deaths** *annually*.
- **New strain** (BI/NAP1) *produces* ***more*** **enterotoxin**, *produces* **binary toxin**, has ***increased*** **sporulation capacity**, and is ***resistant*** to **Fluoroquinolones**. ***Increased*** **risk** of **Metronidazole** ***failure***, ***morbidity***, and ***mortality***.



Endoscopic visualization of pseudomembranous colitis (adherent, yellowish white plaques on the intestinal mucosa)

- ***Risk factors***;
  - * **Antibiotic exposure** for ***extended periods***.
  - * **Hospitalized patients**.
  - * **Advanced age** (>60 y).
  - * **Immunocompromised patients**.
  - * **Medications**; **Proton pump inhibitors** and **Antidepressants**.
- ***Symptoms***:
  - * **Watery diarrhea**.
  - * **Abdominal pain**.
  - * **Leukocytosis** (***increase*** **number** of **WBCs**).
  - * **Gastrointestinal tract** ***complications***.
- ***Pharmacotherapy*** (***Recommendations***);
  - * *For* **mild/moderate CDI**; **Metronidazole 500 mg** *orally* **3 times** *per* **day** for **10 days**.
  - * *For* **severe CDI**; **Vancomycin 125 mg** *orally* **4 times** *per* **day** for **10 days**.
    OR **Fidaxomicin 200 mg** *orally* **twice** ***daily*** for **10 days**.
    - * *Consider* **Rifaximin 400 mg** ***twice*** **daily** for **14 days** OR **Nitazoxanide 500 mg** ***twice*** **daily** for **10 days**.
  - * *For* **severe** and **complicated CDI**;
    - * **Patient** *with* ***no significant*** **abdominal distention**; **Vancomycin 125 mg** *orally* **4 times** a **day** PLUS **Metronidazole 500 mg IV 3 times** a **day**.
    - * **Patient** with **ileus** or **toxic colon** and/or ***significant*** **abdominal distention**; **Vancomycin 500 mg** *orally* **4 times** *per* **day** and **Vancomycin 500 mg** per *rectum* in a **volume** of **500 ml 4 times** *per* **day**) PLUS **Metronidazole 500 mg IV 3 times** a **day**.
  - * *For* **second** and **third recurrences**;
    - * *Consider* **Fidaxomicin** if ***not already*** **given**.
    - * *Consider* ***higher doses*** of **Vancomycin** (**500 mg** *orally* **4 times** a **day**).
    - * **Taper therapy**; **Vancomycin 125 mg** *orally* **4 times** a **day** for **14 days** → *then* **twice** ***daily*** for **7 days** → *then* ***daily*** for **7 days**.
    - * **Pulsed therapy**: **Vancomycin 125 mg** *orally for* **10–14 days** → *then* ***every*** **other day** *for* **8 days** → *then* ***every*** **3 days** *for* **15 days**.

I) Antimicrobials Prophylaxis in Surgery

- Surgical site infections are the *most common* nosocomial infections in surgical patients, accounting for *approximately* 500,000 infections *annually*.
- *Clinical Recommendations*;
  - * Perioperative antibiotic *should be* infused *within* 1 hour *before* incision or *within* 2 hours if the patient is *receiving* Vancomycin or Fluoroquinolones.
  - * Perioperative antibiotic *prophylaxis should be* consistent with *published* guidelines.
  - * Perioperative antibiotic *prophylaxis should* generally be discontinued *within* 24 hours *after* surgery completion (*within* 48 hours for cardiothoracic surgery).
- *Antimicrobials Prophylaxis* to *Prevent Surgical Site Infections*;

System	Organ	Regimens
GIT	Gastric or Duodenal	* Recommendation; Cefazolin. * Alternative; *Patients with β-lactam allergy*; Clindamycin OR Vancomycin. PLUS Gentamicin OR Aztreonam OR Fluoroquinolone.
	Biliary	* Recommendation; Cefazolin * Alternative; Ampicillin/Sulbactam OR Cefotetan OR Cefoxitin OR Ceftriaxone. * Alternative; *Patients with β-lactam allergy*; - Clindamycin OR Vancomycin PLUS Gentamicin OR Aztreonam OR Fluoroquinolone. - Metronidazole PLUS Gentamicin OR Fluoroquinolone.
	Appendectomy	* Recommendation; Cefoxitin OR Cefotetan OR Cefazolin PLUS Metronidazole. * Alternative; *Patients with β-lactam allergy*; - Clindamycin PLUS Gentamicin OR Aztreonam OR Fluoroquinolone. - Metronidazole PLUS Gentamicin OR Ciprofloxacin OR Levofloxacin.
	Small Intestine	* Recommendation; *Without* obstruction; Cefazolin. ; *With* obstruction; - Cefoxitin OR Cefotetan. - Cefazolin PLUS Metronidazole. * Alternative; *Patients with β-lactam allergy*; - Clindamycin PLUS Gentamicin OR Aztreonam OR Fluoroquinolone - Metronidazole PLUS Gentamicin OR Ciprofloxacin OR Levofloxacin
	Hernioplasty and Herniorrhaphy	* Recommendation; Cefazolin. ; *For* MRSA; Vancomycin. * Alternative; *Patients with β-lactam allergy*; - Clindamycin PLUS Vancomycin.
	Colorectal	* *Combined* oral and parenteral regimens is better *than* parenteral regimens *alone*. * Recommendation Parenteral Regimens; 1 dose. - Cefoxitin OR Cefotetan OR Cefazolin PLUS Metronidazole. - IF *high* resistance; Ceftriaxone PLUS Metronidazole. - Alternative; Ampicillin/Sulbactam. - Alternative; *Patients with β-lactam allergy*; - Clindamycin PLUS Aminoglycoside OR Aztreonam OR Fluoroquinolone. - Metronidazole PLUS Aminoglycoside OR Fluoroquinolone. * Recommendation Oral Regimens; 2 to 3 doses. - Neomycin Sulfate PLUS Erythromycin Base; 19, 18, and 9 hours *before* surgery. - Neomycin Sulfate PLUS Metronidazole; 13 and 9 hours *before* surgery.

Head and Neck Procedures	A) If *placement* of prosthetic material; * Recommendation; Cefazolin OR Cefuroxime. * Alternative; *Patients with β-lactam allergy*; Clindamycin. B) If clean *contaminated* head and neck procedures; * Recommendation; - Cefazolin OR Cefuroxime PLUS Metronidazole. - Ampicillin/Sulbactam. * Alternative; *Patients with β-lactam allergy*; - Clindamycin +/- Aminoglycoside (if Gm -ve)
Neurosurgery Procedures	* Recommendation; Cefazolin. ; *For* MRSA; Vancomycin. * Alternative; *Patients with β-lactam allergy*; - Clindamycin +/- Vancomycin (if MRSA).
Obstetrics and Gynecology	A) Cesarean Delivery Procedures; * Recommendation; Cefazolin. * Alternative; *Patients with β-lactam allergy*; - Clindamycin PLUS Gentamicin. B) Hysterectomy Procedures; * Recommendation; Cefazolin. * Alternative; Cefoxitin OR Cefotetan OR Ampicillin/Sulbactam. * Alternative; *Patients with β-lactam allergy*; - Clindamycin OR Vancomycin PLUS Aminoglycoside OR Aztreonam OR Fluoroquinolone. - Metronidazole PLUS Aminoglycoside OR Fluoroquinolone.
Ophthalmic Procedures	* Preoperative antisepsis *with* povidone–iodine is *recommended*. * Topical antimicrobials include; one drop *every* 5–15 minutes for 5 doses *within* the 1 hour *before* the start of the procedure; - Neomycin/Polymyxin B/Gramicidin solution (Neosporin®). OR - Fluoroquinolones; Gatifloxacin (Zymar®) OR Moxifloxacin (Vigamox®). * Addition of *sub-conjunctival* Cefazolin 100 mg OR *intra-cameral* Cefazolin 1–2.5 mg OR Cefuroxime 1 mg at the *end* of the procedure is *optional*.
Orthopedic Procedures	A) Clean Orthopedic Procedures *Not* Involving Implantation of Foreign Materials; Antimicrobial prophylaxis is *not recommended*. B) Spinal Procedures *with* and *without* Instrumentation, C) Hip Fracture Repair and D) Total Joint Replacement; * Recommendation; Cefazolin. * Alternative; Clindamycin OR Vancomycin. * If there are Gm -ve organisms; - Clindamycin OR Vancomycin PLUS Cefazolin. - *β-lactam allergy*; Clindamycin OR Vancomycin PLUS Aztreonam OR Gentamicin OR Fluoroquinolone. * Mupirocin *should be* given *intra-nasally* to *all patients* known to be colonized with *Staphylococcus aureus*.
Urologic Procedures	* Antimicrobial prophylaxis is *recommended only* if patients with risk factors for infection. A) For patients *undergoing* lower urinary tract instrumentation *with risk factors* for infection; Recommendation; Fluoroquinolone OR Trimethoprim/Sulfamethoxazole (Oral or IV) OR Cefazolin (IV or IM). B) For patients *undergoing* clean urologic procedures *without* entry into UT; * Recommendation; Cefazolin. * Alternative; *β-lactam allergy*; Clindamycin OR Vancomycin. C) For patients *undergoing* clean urologic procedures *with* entry *into* UT; * Recommendation; Cefazolin. * Alternative; - Fluoroquinolone PLUS Aminoglycoside PLUS Metronidazole. - Fluoroquinolone PLUS Aminoglycoside PLUS Clindamycin. D) For *clean*-contaminated *procedures* of the urinary tract (often entering the GIT), antimicrobials as recommended for elective colorectal surgery are *recommended*.